A NEW APPROACH TO THE TOTAL SYNTHESIS OF HARRINGTONOLIDE

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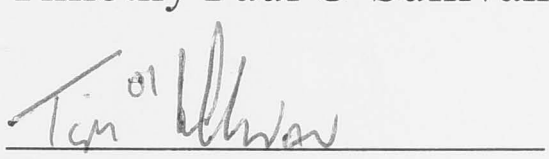
DECLARATION

This thesis contains no material previously submitted for a degree in any other University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

Timothy Paul O'Sullivan



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ABSTRACT

This thesis describes studies towards the total synthesis of the biologically active diterpene harringtonolide. This complex secondary metabolite contains a structurally interesting tropone functionality and also possesses seven stereogenic centres, six of which are located on a single cyclohexane ring in the molecule. In the first chapter, a review of the strategies used previously for the synthesis of harringtonolide is provided. A new approach is proposed, based on the strategy of a Diels-Alder reaction between a 2-pyrone and an indenone followed by an intramolecular cyclopropanation of the aromatic ring.

The initial approach based on a mercury-mediated cyclopropyl ring-opening reaction is outlined in Chapter 2. It was discovered that the alkene moiety in the first 2-pyrone/indenone cycloadduct that was prepared was surprisingly unreactive, and severely limited the number of possible approaches for the elaboration of the C-ring substituents in harringtonolide, thus necessitating a reappraisal of the original synthetic plan. Frontier molecular orbital calculations are presented in order to provide a theoretical basis for the observed experimental regioselectivity of the [4+2] cycloadditions.

In Chapter 3, methods for the incorporation of a methyl group into the parent pyrone is described. The methodology for manipulation of the bridge stereochemistry, installation of the internal ether bond and homologation of the carboxy ester through to an advanced α-diazoketone intermediate is detailed. The attempted intramolecular arene cyclopropanation is also discussed.

A strategy to mask the lactone carbonyl and thus prevent ylide formation with the diazoketone derived carbenoid functionality was also explored. The results from the choice of various protecting groups are reported in Chapter 4 as well as the effect of the alteration of the side chain on the overall reactivity of the molecule.

Efforts towards the incorporation of oxygen into the C11 position are outlined in Chapter 5. This culminated in a highly convergent and efficient synthetic route involving a Diels-Alder reaction of a 5-methoxy substituted 2-pyrone. Chapter 6 discusses this work and possible future directions.

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ABBREVIATIONS

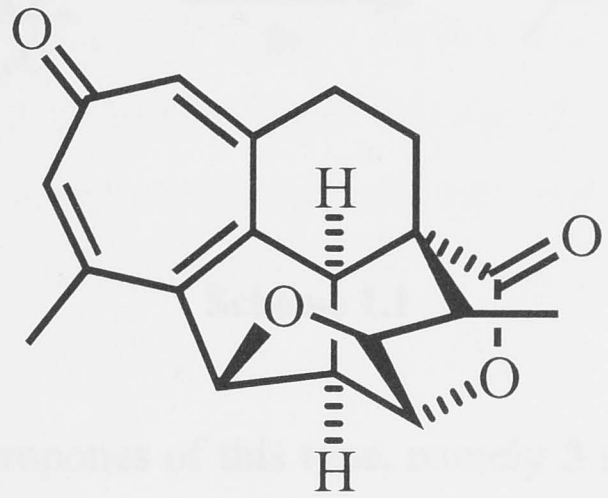
The following abbreviations have been used throughout this thesis

Ac	acetyl
acac	acetylacetonate
acam	acetamide
AIBN	azobisisobutyronitrile
Ar	aryl
Bu	butyl
m-CPBA	*m*-chloroperoxybenzoic acid
^{13}C-NMR	Carbon-13 Nuclear Magnetic Resonance
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
EI	Electron Impact
Et	ethyl
HETCOR	Heteronuclear Correlation Spectroscopy
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
^{1}H-NMR	Proton Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectroscopy
IR	Infrared
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	Low Resolution Mass Spectroscopy
Me	methyl
MHz	megahertz
m.p.	melting point

NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	Nuclear Magnetic Resonance
OTf	triflate
Ph	phenyl
ppm	parts per million
PPA	polyphosphoric acid
Pyr	pyridine
TAO	triethylamine *N*-oxide
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
THT	tetrahydrothiophene
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic Acid
TsO	tosylate

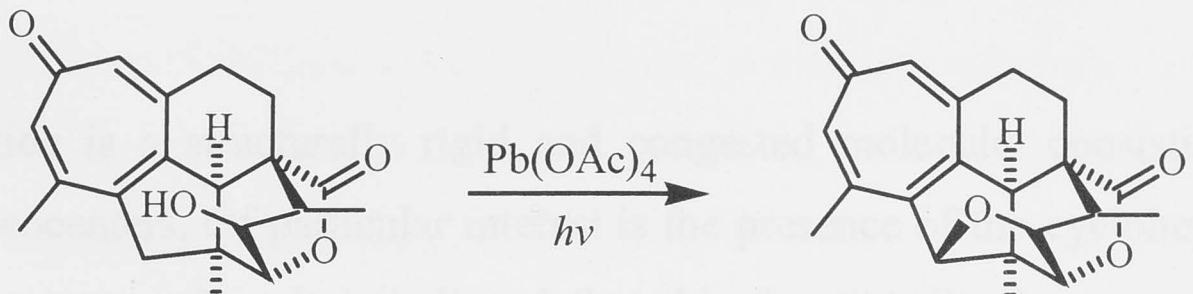
Chapter One

Introduction



SECTION 1.1 Introduction

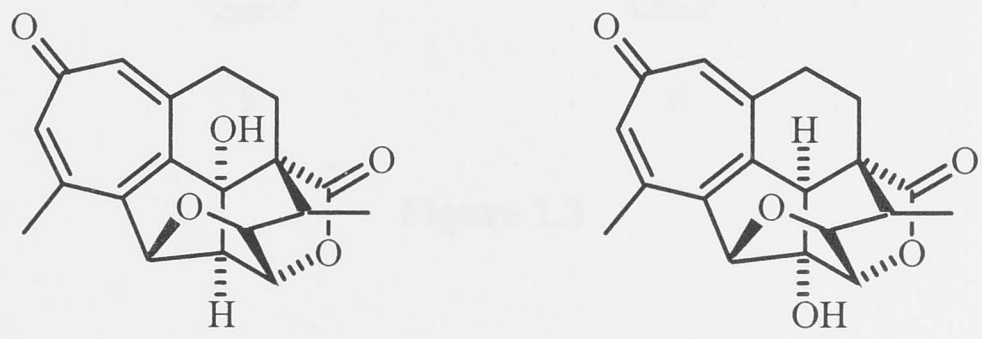
The diterpenoid tropone, harringtonolide (**1**), was first isolated in North America from the seeds of *Cephalotaxus harringtonia* (Taxaceae) and its structure established by X-ray crystallography.[1] At about the same time, **1** was independently discovered in the bark of the related Chinese species *Cephalotaxus hainanensis* and given the name hainanolide.[2] It was found to have both anti-neoplastic and anti-viral properties, being active against Lewis Lung carcinoma, Walker carcinoma, Sarcoma-180, and L-1210, L-615 and P-388 leukaemias, as well as showing *in vitro* activity against influenza type A, Newcastle disease, Japanese B encephalitis and vaccinia viruses.[3] In *C. hainanensis*, **1** was accompanied by the closely related, but biologically inactive carbinol, hainanolidol (**2**), the structure of which was established through its conversion to **1** by transannular oxidation with lead tetraacetate (Scheme **1.1**).[4]



2 **1**

Scheme 1.1

More recently, two further tropones of this type, namely **3** and **4,** have been discovered in *C. fortunei*.[5]



3 **4**

Figure 1.1

The genus *Cephalotaxus sp.* is comprised of 10 species, eight of which are found in China,[6] and is a member of the plant family Taxacaeae, which also includes the genus Taxus (collectively known as yew trees). The yews have been a rich source of a variety of structurally diverse and biologically active diterpenes and have generated great interest in pharmacology, botany and organic synthesis. Chief among these has been the diterpene, Taxol, which was isolated from the bark of the Pacific yew tree, and which shows considerable potential as an antitumour agent (Figure **1.2**).[7,8]

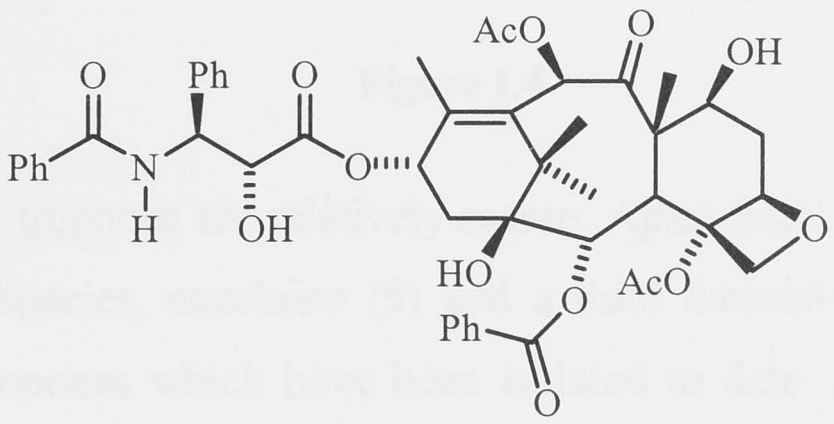


Figure 1.2

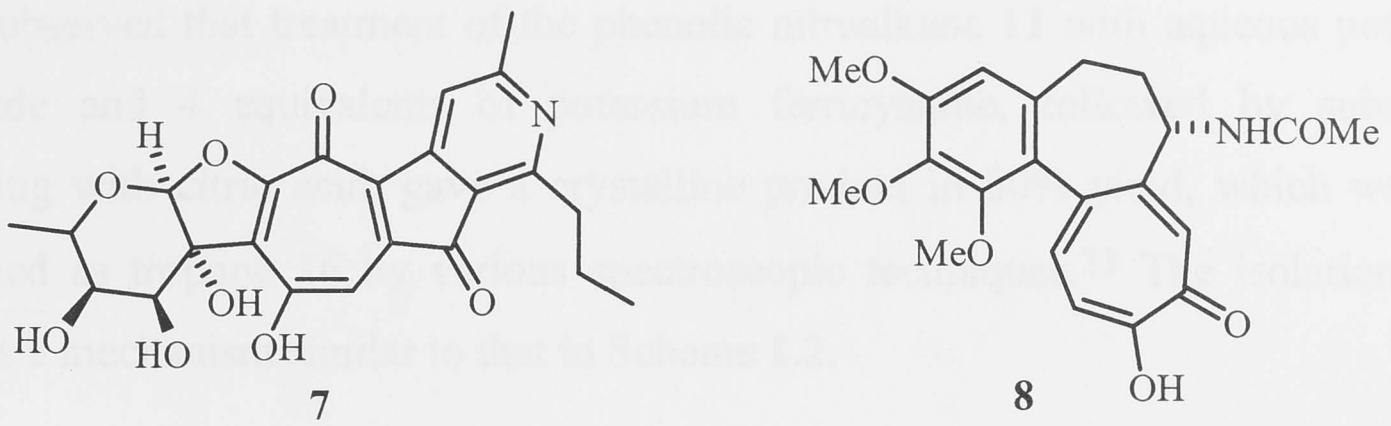
Harringtonolide is a structurally rigid and congested molecule, consisting of seven adjacent stereocenters. Of particular interest is the presence of the cycloheptatrienone - or tropone moiety – since it is believed that this functionality is responsible for the biological activity of the compound. The structurally interesting tropone moiety (**5**), more commonly found as 2-hydroxytropone (**6**) (or tropolone), is incorporated into a large group of natural products from a wide range of biological sources.

5 **6**

Figure 1.3

Tropolones are quite prevalent in nature and account for more than 95% of the *ca.* 92 known troponoid natural products. They range in complexity from **6** itself (*Pseudomonas plantarii*),[9] which shows broad-spectrum bactericidal activity,[10] to more complex systems such as rubrulone (**7**) (from *Staphylococcus echinoruber*),[11,12] a food colouring agent, and colchicine (**8**)[13,14] (mainly from *Colchicum sp.*),[15] which has been

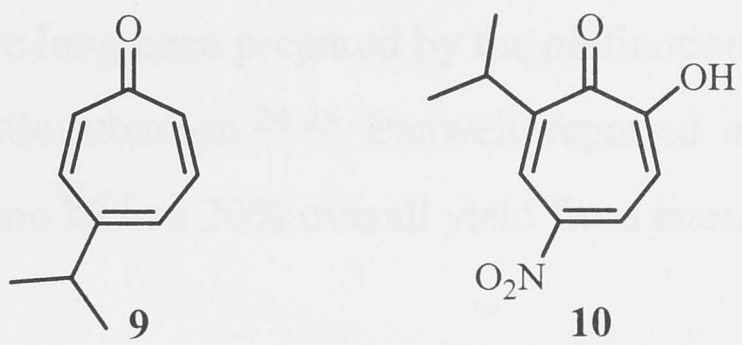
used extensively in the treatment of gout,[16,17] and also has potential in the treatment of cancer.



7 **8**

Figure 1.4

In contrast, the parent tropones are relatively scarce. Apart from the compounds found in the *Cephalotaxus* species, nezukone (**9**) and a thiol derivative are the only other naturally occurring tropones which have been isolated to date. Nezukone, which has been synthesised in three laboratories,[18-20] is found in *Thuja sp.*[21] and seems to provide the parent plant with some measure of protection against fungal infection. In addition, a number of simple artificial troponoids have been synthesised, either for their theoretical interest[22] or for their potential biological activity. For example, **10** shows remarkable antibacterial activity against a variety of gram negative and gram positive bacteria.[10]

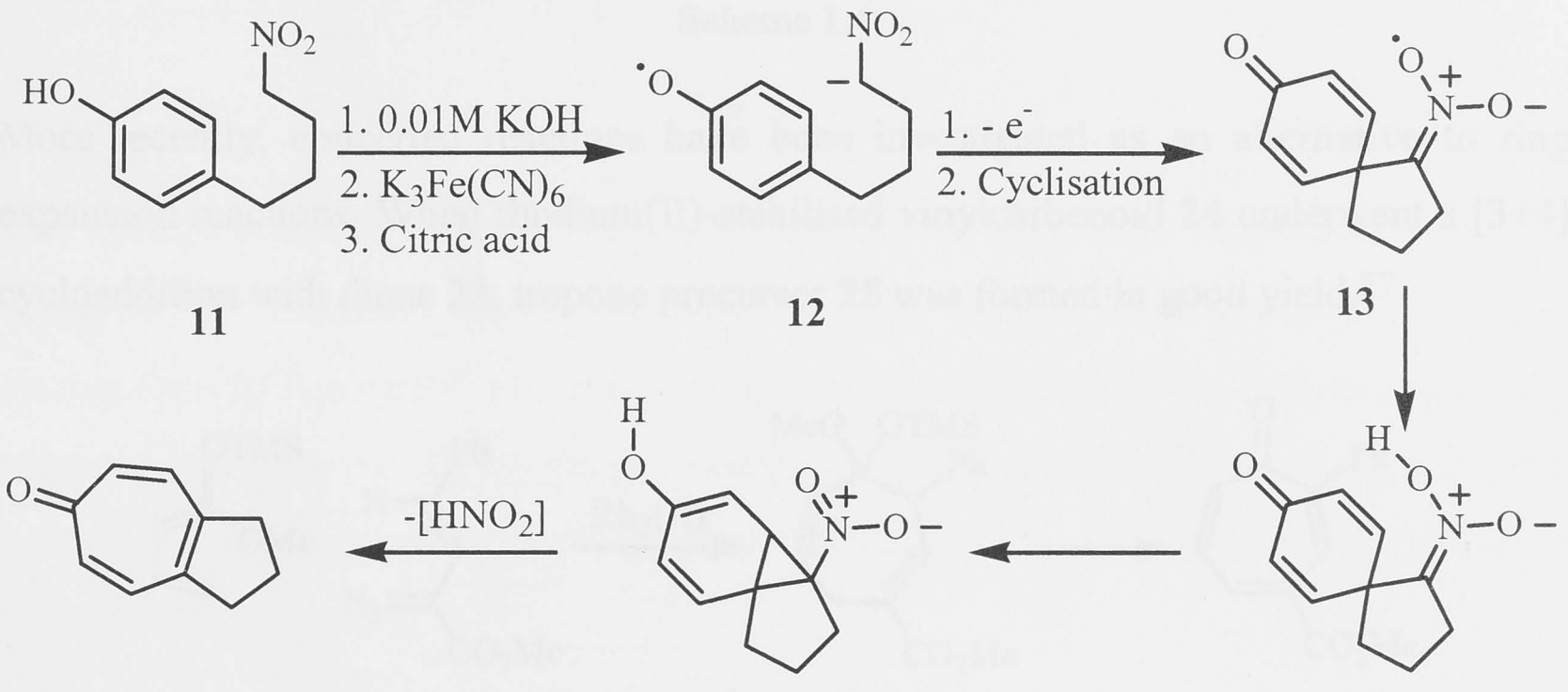


9 **10**

Figure 1.5

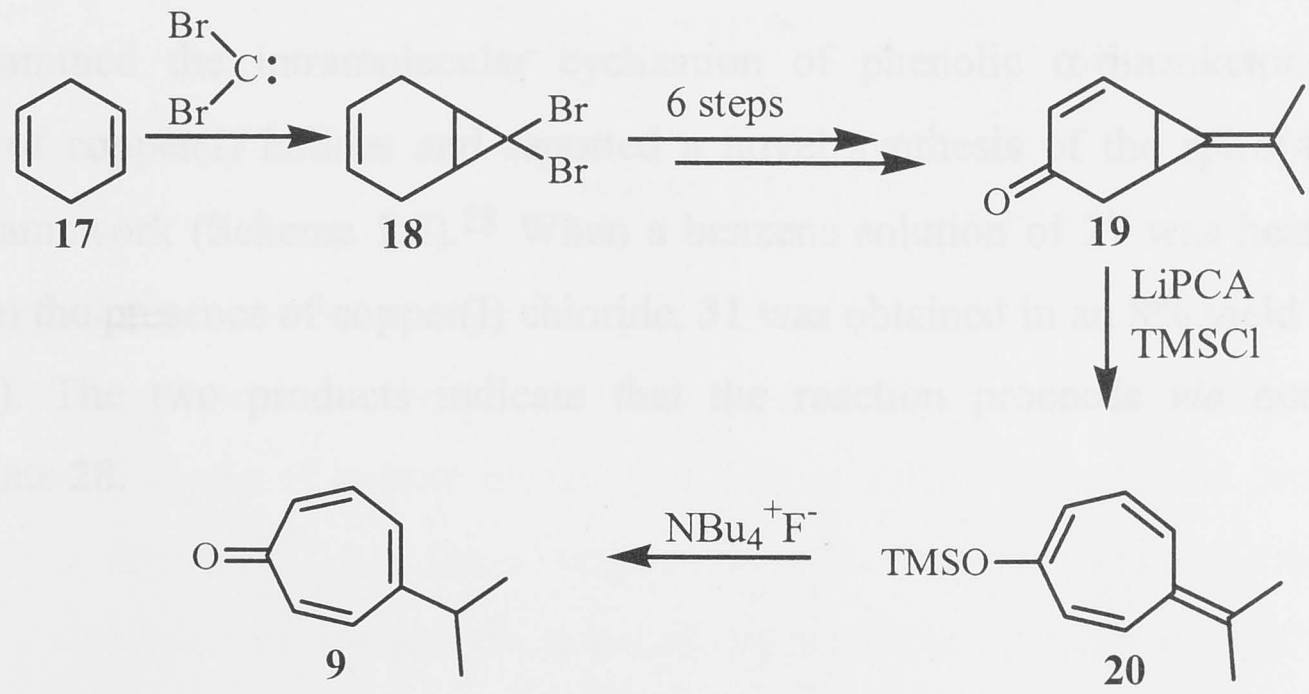
SECTION 1.2 Tropone Formation

Kende observed that treatment of the phenolic nitroalkane **11** with aqueous potassium hydroxide and 4 equivalents of potassium ferricyanide, followed by subsequent quenching with citric acid, gave a crystalline product in 80% yield, which was later confirmed as tropone **16** by various spectroscopic techniques.[23] The isolation of **13** suggests a mechanism similar to that in Scheme **1.2**.



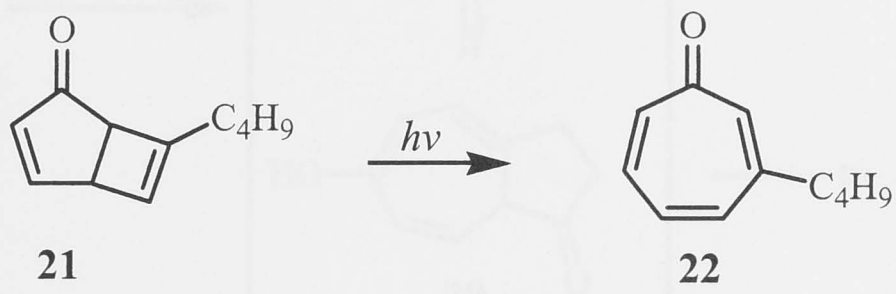
Scheme 1.2

While heptafulvenes have long been prepared by the olefination of tropones, the reverse process has received little attention.[24,25] Banwell reported an efficient synthesis of Nezukone *via* heptafulvene **20** in a 20% overall yield from enone **19** (Scheme **1.3**).[18]



Scheme 1.3

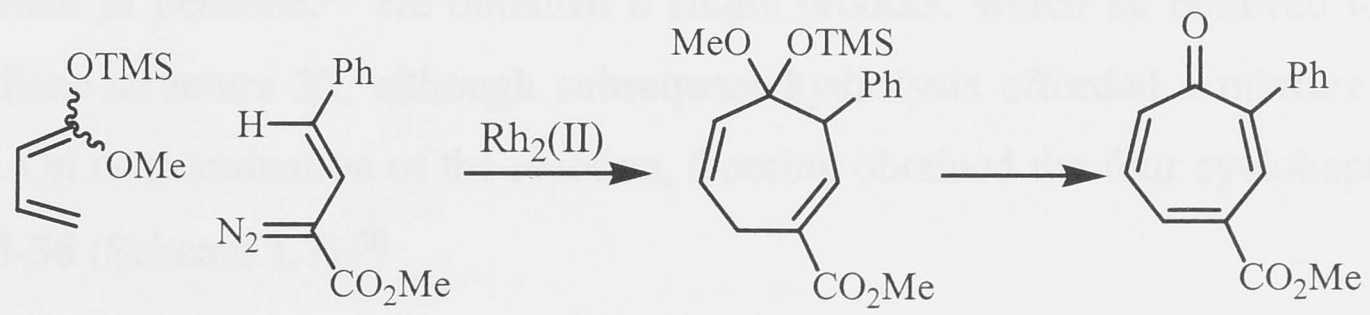
While there are many synthetic routes available to 2-alkyl- and 2-aryl-tropones, methods for preparing 3-alkyltropones remain relatively scarce. Cavazza *et al.* have developed a novel synthesis of tropone **22** utilising a light-induced oxa-di-π-methane rearrangement of diene **21** (Scheme **1.4**).[26]



21 **22**

Scheme 1.4

More recently, concerted reactions have been investigated as an alternative to ring expansion reactions. When rhodium(II)-stabilised vinylcarbenoid **24** underwent a [3+4] cycloaddition with diene **23**, tropone precursor **25** was formed in good yield.[27]

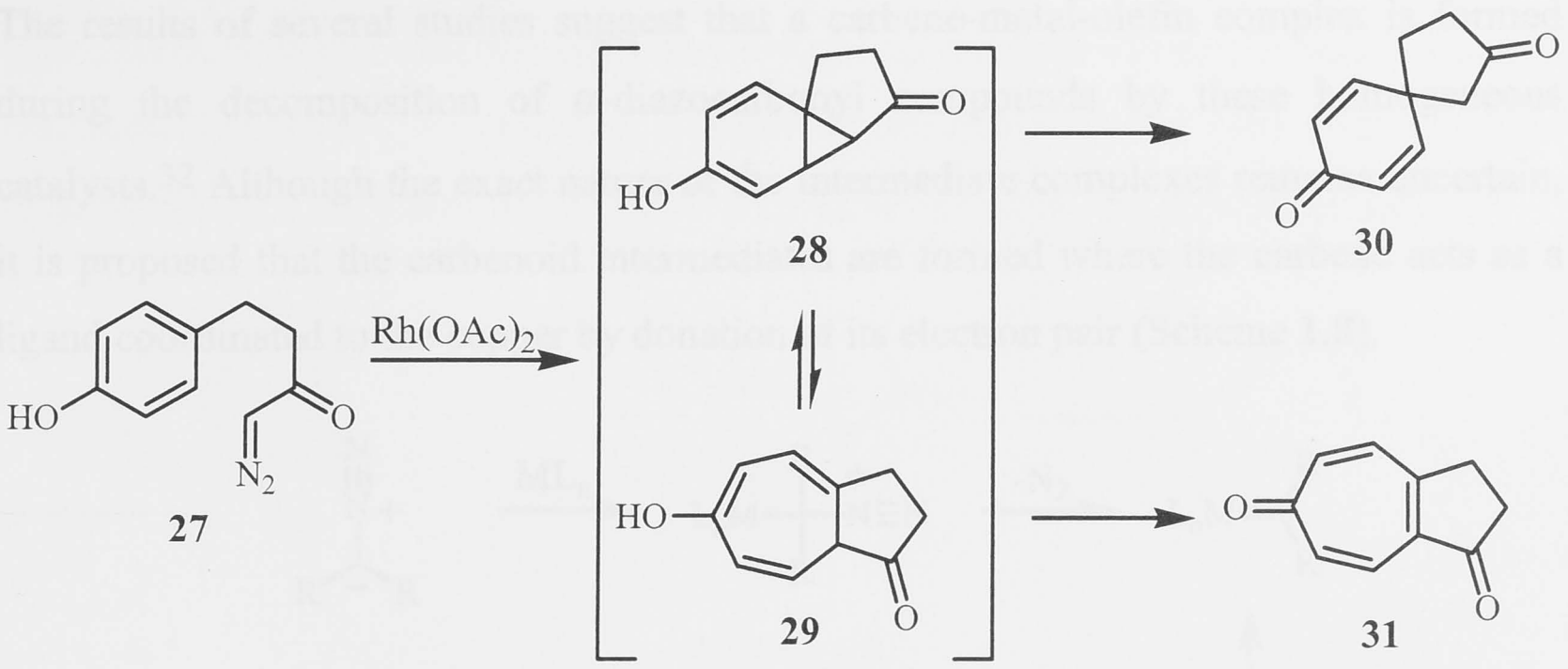


23 **24** **25** **26**

Scheme 1.5

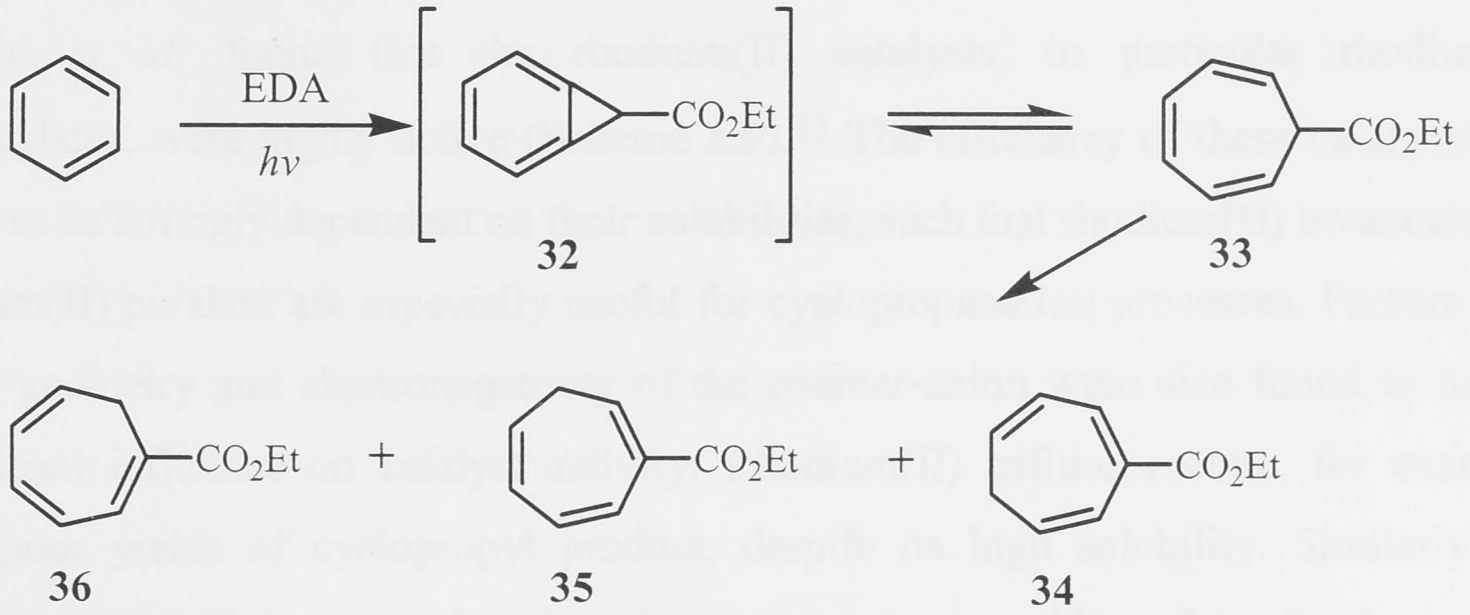
The most popular methods of synthesising tropones, however, usually involve the formation of an unstable norcaradiene by attack of carbenoids or other suitable species onto a benzenoid or reduced benzenoid ring, followed by rearrangement and subsequent ring expansion.

Iwata examined the intramolecular cyclisation of phenolic α-diazoketones in the presence of copper(I) halides and reported a novel synthesis of the spiro[4.5]decane carbon framework (Scheme **1.6**).[28] When a benzene solution of **27** was heated for 20 minutes in the presence of copper(I) chloride, **31** was obtained in an 8% yield as well as **30** (34%). The two products indicate that the reaction proceeds *via* norcaradiene intermediate **28**.



Scheme 1.6

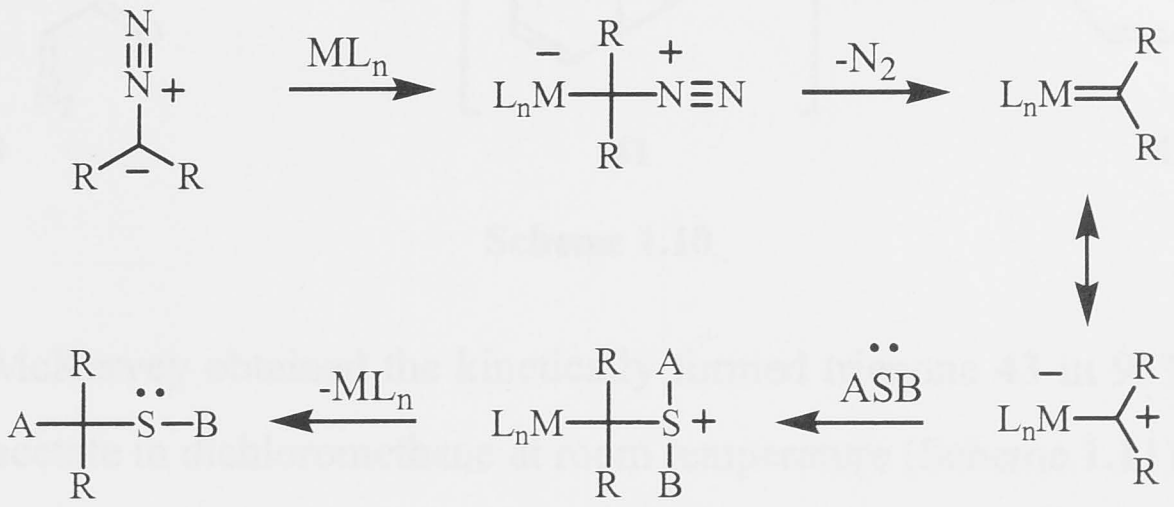
The cyclopropanation of aromatic rings using α-diazocarbonyl compounds was first observed by Buchner while investigating the thermal decomposition of ethyl diazoacetate in benzene.[29] He obtained a single product, which he believed to be the norcaradiene structure **32**, although subsequent hydrolysis afforded a mixture of four isomers. On re-examination of the reaction, Doering obtained the four cycloheptatrienyl esters **33-36** (Scheme **1.7**).[30]



Scheme 1.7

These thermal and photochemical processes usually lead to complex mixtures of products in low yields, a result of the generation of highly reactive carbene intermediates. The use of copper bronze and copper sulfate as catalysts proved to be more synthetically useful, but these reagents were in turn superseded by the soluble copper chelates, such as bis(acetylacetonato) copper(II), introduced by Nozaki in the 1960s.[31]

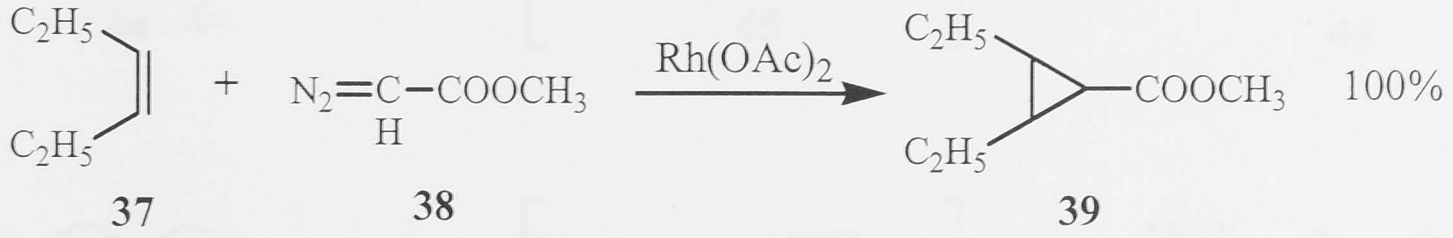
The results of several studies suggest that a carbene-metal-olefin complex is formed during the decomposition of α-diazocarbonyl compounds by these homogeneous catalysts.[32] Although the exact nature of the intermediate complexes remains uncertain, it is proposed that the carbenoid intermediates are formed where the carbene acts as a ligand coordinated to the copper by donation of its electron pair (Scheme **1.8**).



Scheme 1.8

Nucleophilic attack by the diazo group onto the electrophilic metal complex leads to nitrogen extrusion. The metal stabilised carbene then reacts with an electron-rich substrate and thus regenerates the catalytic species.

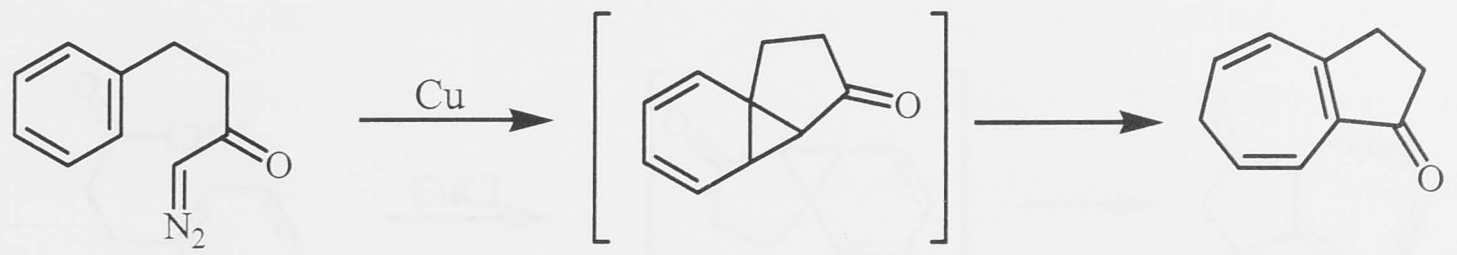
Teyssié *et al.* found that the rhodium(II) catalysts, in particular rhodium(II) carboxylates, were highly active (Scheme **1.9**).[33] The efficiency of these catalysts was found to be strongly dependent on their solubilities, such that rhodium(II) butanoate and rhodium(II) pivalate are especially useful for cyclopropanation processes. Factors such as the geometry and electronegativity of the counter-anion were also found to have a significant influence on catalyst activity. Rhodium(II) trifluoroacetate, for example, gave poor yields of cyclopropyl product, despite its high solubility. Similarly, the oxidation state of rhodium played an important role, as evidenced by the low yields obtained in the presence of rhodium(III) pivalate and rhodium(I) complexes.



37 **38** **39**

Scheme 1.9

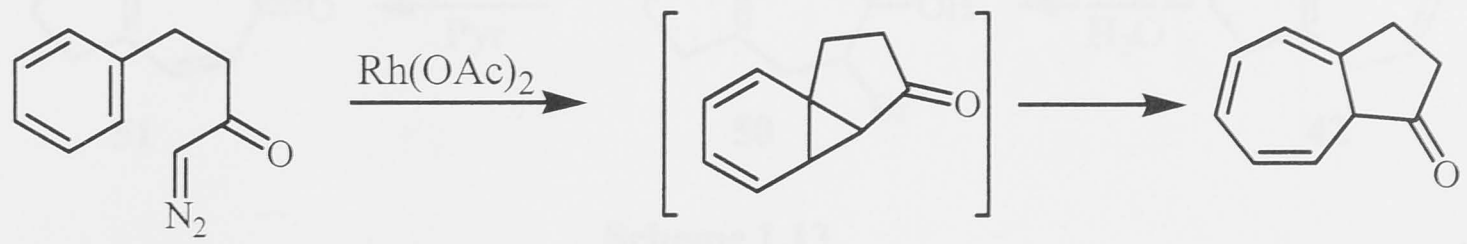
The discovery of this rhodium chemistry opened up the field of intramolecular Buchner reactions. Previously, treatment of 1-diazo-4-phenylbutan-2-one (**40**) with a copper catalyst afforded the thermodynamic product **42** in only 13% yield (Scheme **1.10**).[34]



40 **41** **42**

Scheme 1.10

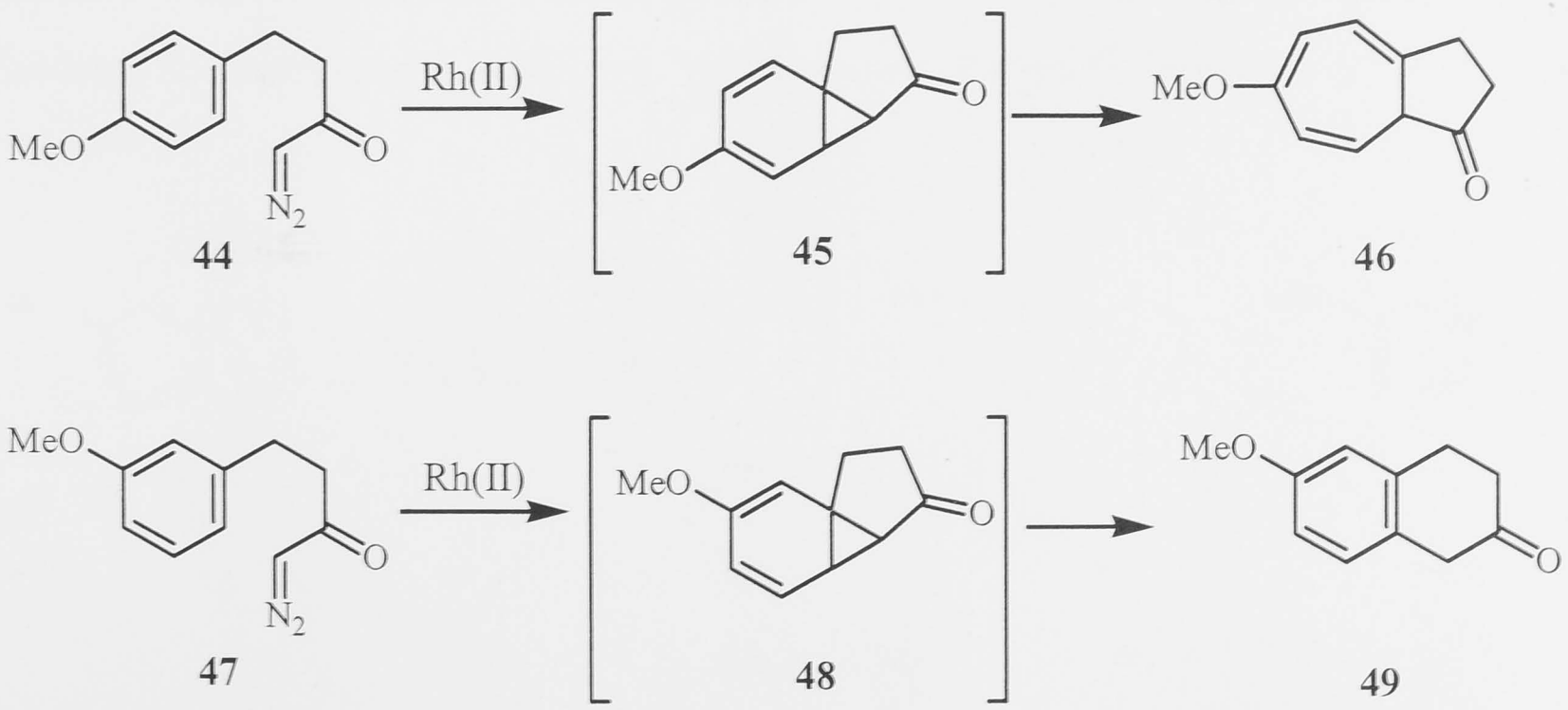
In contrast, McKervey obtained the kinetically formed trienone **43** in 95% yield using rhodium(II) acetate in dichloromethane at room temperature (Scheme **1.11**).[35]



40 **41** **43**

Scheme 1.11

McKervey also applied this methodology to a range of diazoketones derived from dihydroxycinnamic acids and obtained high yields of various tetrahydroazulenones.[36] He found that in the absence of an electron donating group in the *meta*-position, electrocyclic ring opening produced the kinetically favoured trienones, such as **46** (Scheme **1.12**). However, a *meta*-methoxy group favours an alternate bond breaking mechanism and formation of tetralone **49**.

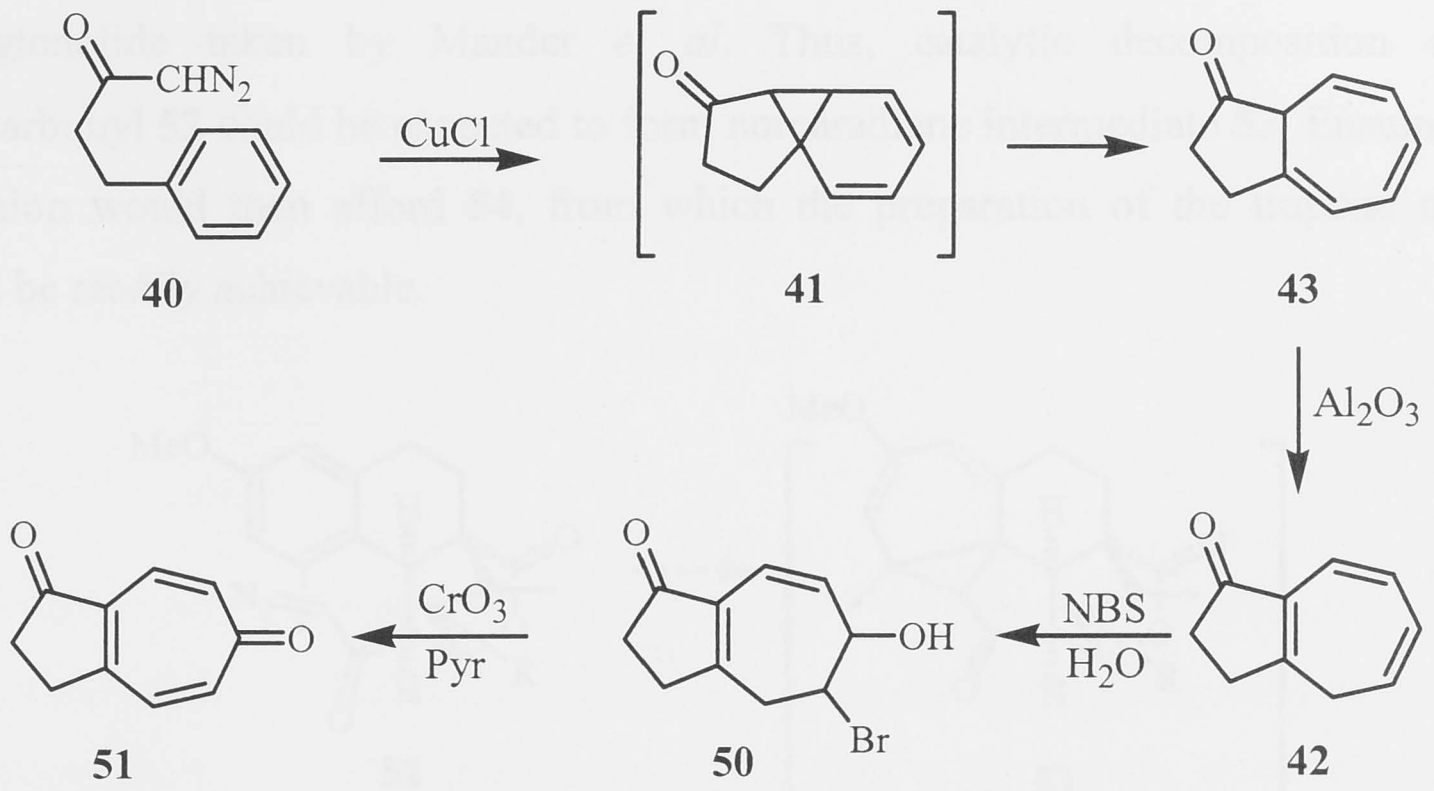


44 **45** **46**

47 **48** **49**

Scheme 1.12

Scott has also been active in this field of research, particularly in the area of azulene synthesis.[37,38] More recently, this work has provided a novel route to tropones (Scheme **1.13**). Bromination of the azulene **42**, derived from diazoketone **40**, gives a single bromohydrin product **50.** Elimination of HBr followed by oxidation leads to tropone **51**.

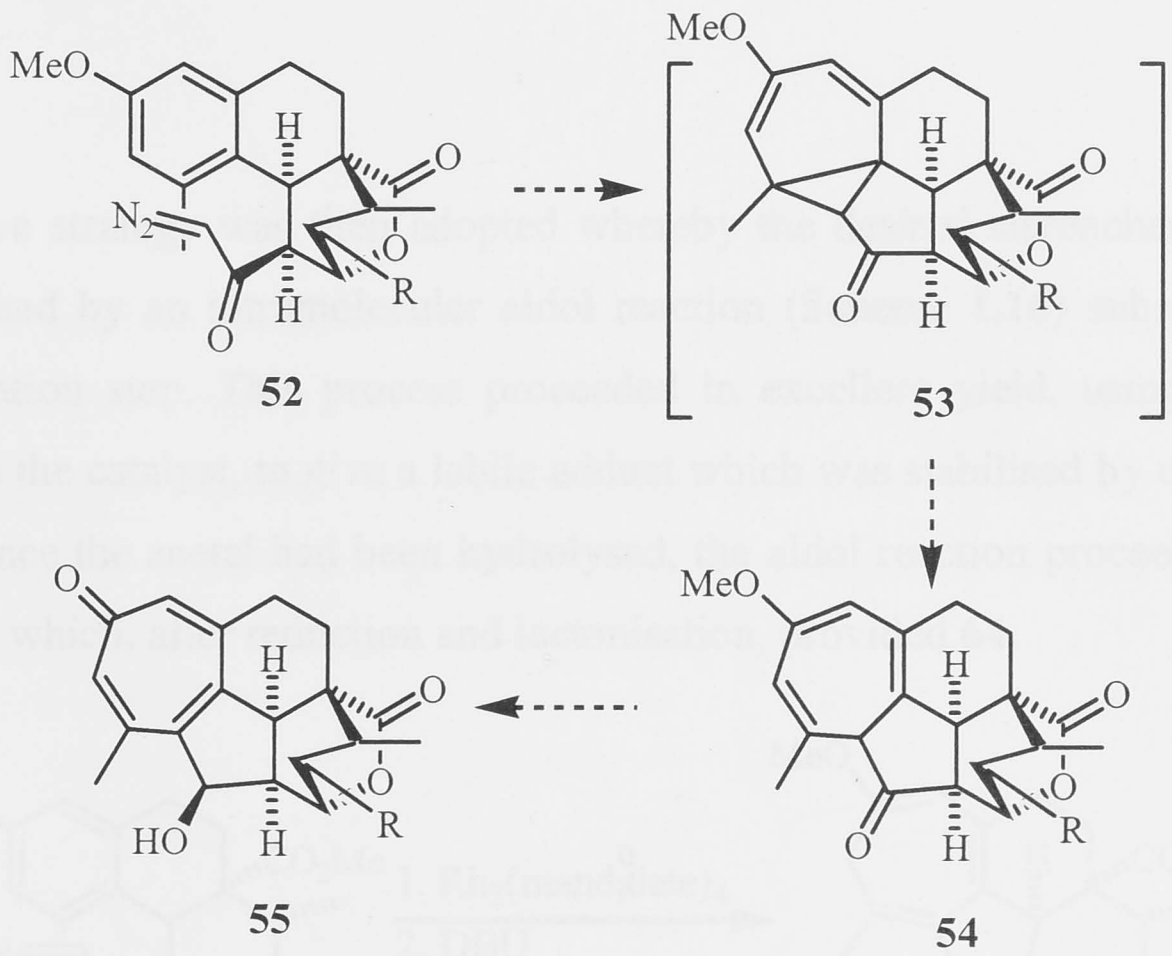


40 **41** **43** **42** **50** **51**

Scheme 1.13

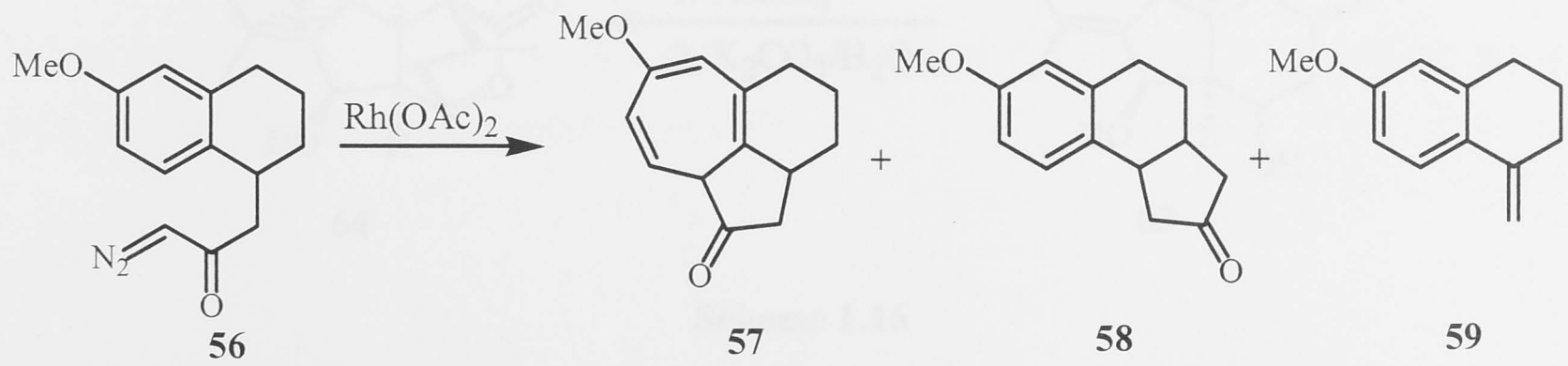
SECTION 1.3 Previous Approaches

With an eye to McKervey's work, an arene cyclopropanation reaction leading to a cycloheptatriene was envisaged as the pivotal step in the first approach to harringtonolide taken by Mander *et al.* Thus, catalytic decomposition of α-diazocarbonyl **52** could be expected to form norcaradiene intermediate **53**. Ensuing ring expansion would then afford **54**, from which the preparation of the tropone moiety should be readily achievable.



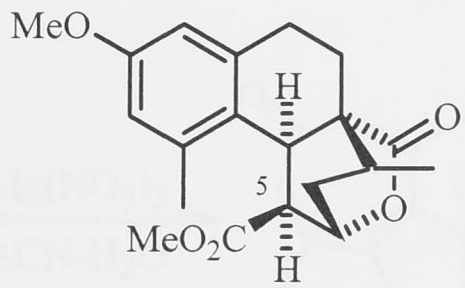
Scheme 1.14

A model study on the reaction of tetralin diazoketone **56** with rhodium(II) acetate afforded only 13% of the desired product **57** (Scheme **1.15**).[39] However, use of rhodium(II) caprolactam, developed by Doyle and Padwa,[40] furnished **57** in a 75% yield.[41]



Scheme 1.15

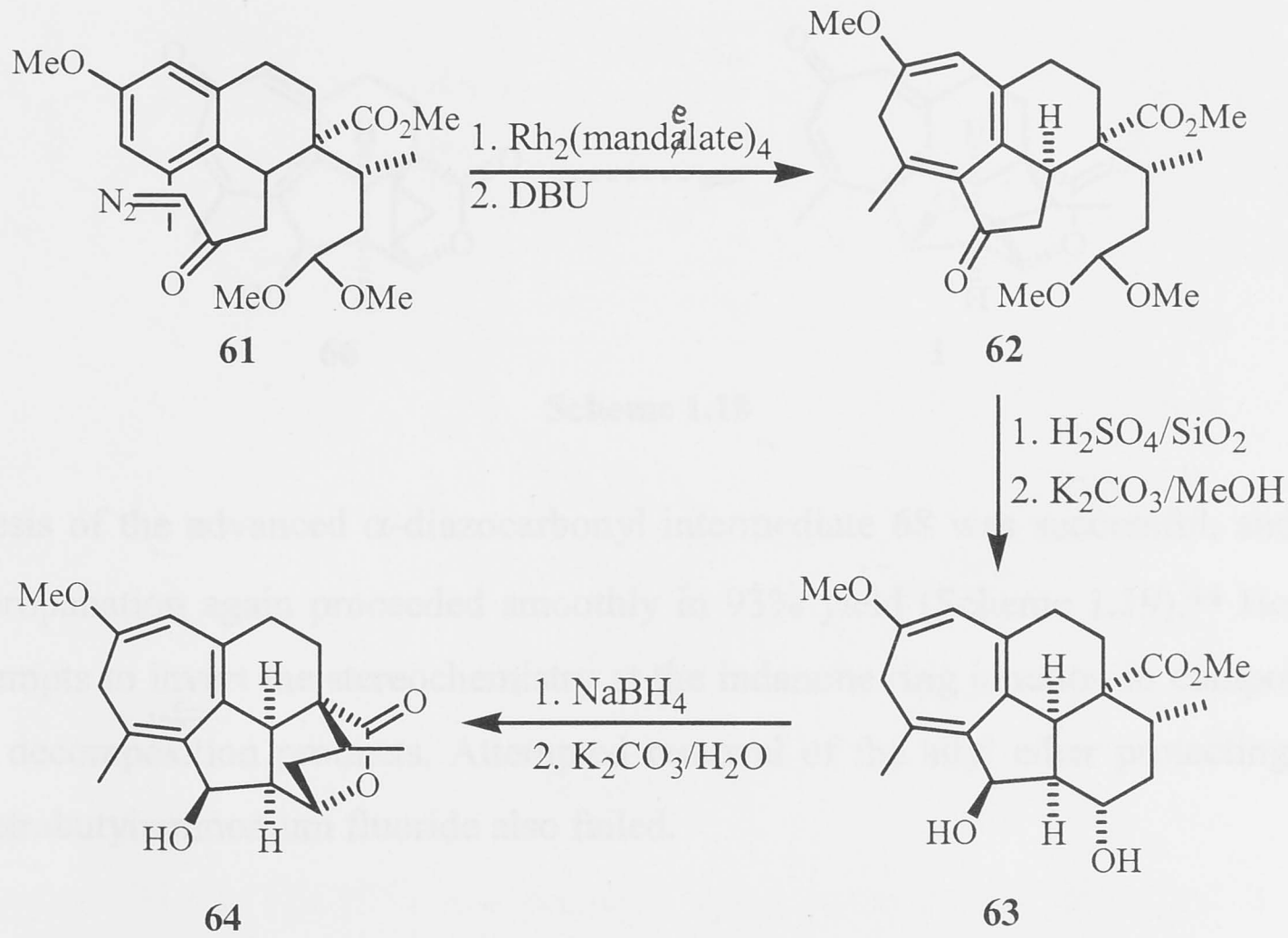
Although **60** could be obtained fairly readily, attempts to obtain the 5β-epimer proved unsuccessful.[42] The 5β-stereochemistry is essential in achieving the geometry required for the subsequent cyclopropanation and this route was accordingly abandoned.



60

Figure 1.6

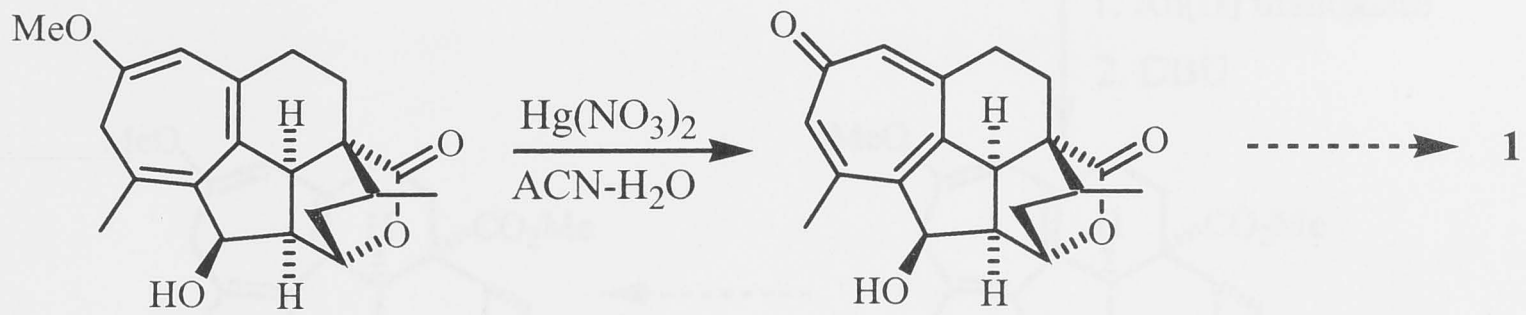
An alternative strategy was then adopted whereby the desired stereochemistry at C-5 was established by an intramolecular aldol reaction (Scheme **1.16**) subsequent to the cyclopropanation step. This process proceeded in excellent yield, using rhodium(II) mandelate as the catalyst, to give a labile adduct which was stabilised by conjugation to afford **62**. Once the acetal had been hydrolysed, the aldol reaction proceeded smoothly to furnish **63** which, after reduction and lactonisation, provided **64**.



61 **62** **63** **64**

Scheme 1.16

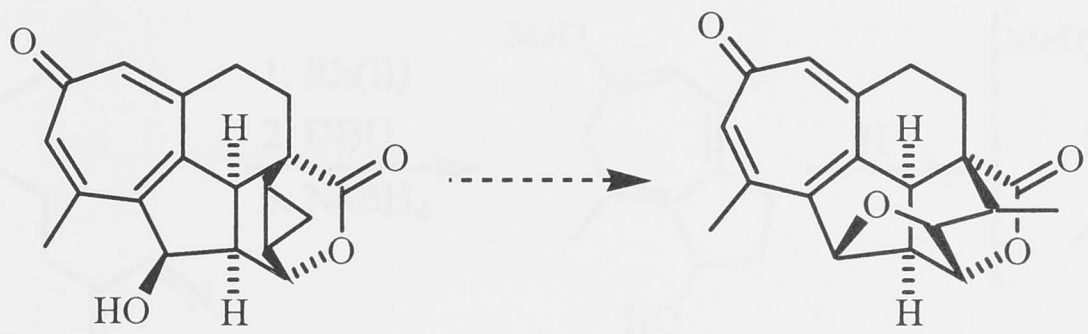
At this point, the tropone functionality was established in a single step by treatment with mercuric nitrate to afford the secoharringtonolide **65**. Unfortunately, all subsequent attempts to form the ether bridge by transannular oxidation, and thus convert **65** into harringtonolide, failed.



64 **65**

Scheme 1.17

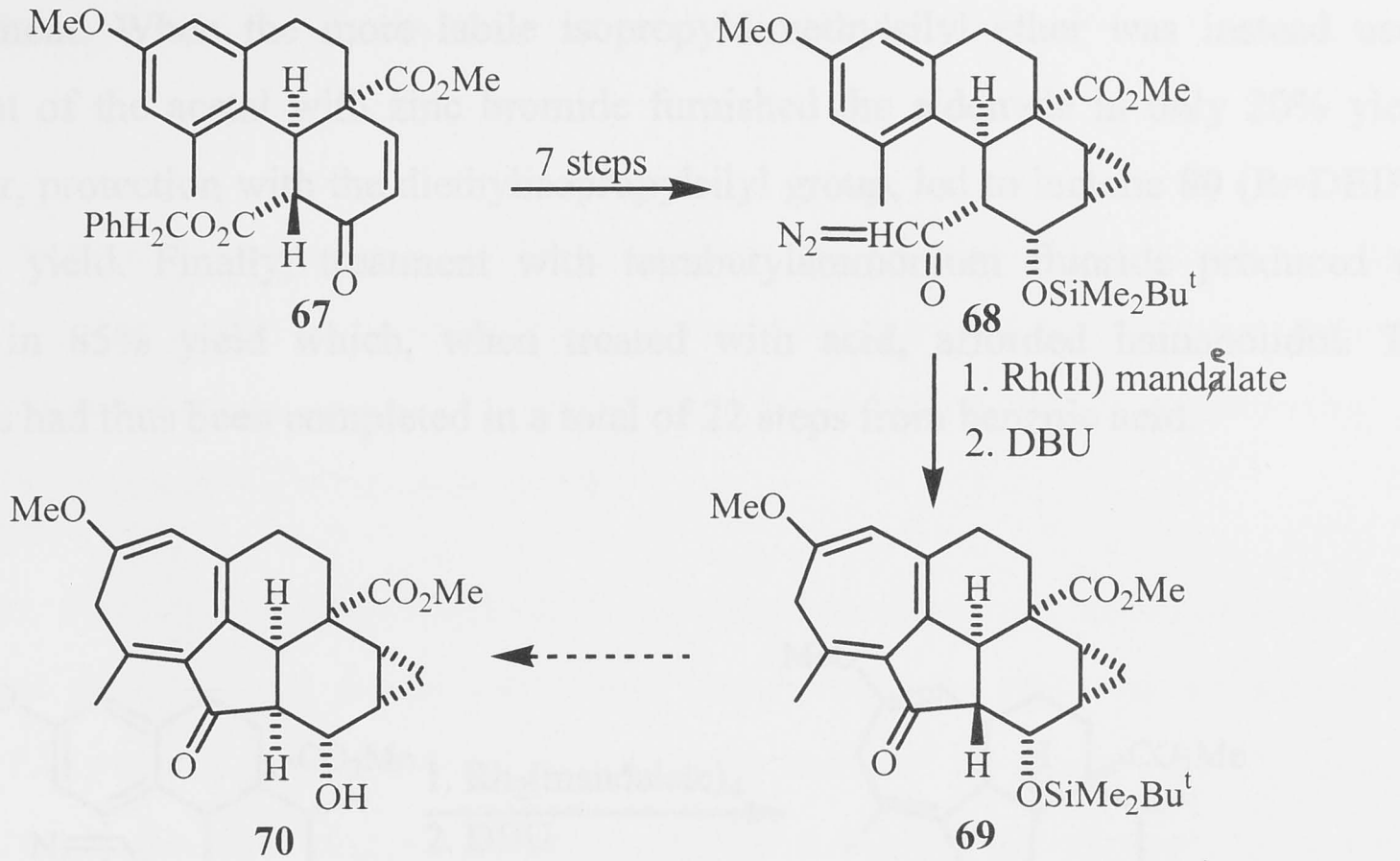
An alternative proposal for the synthesis of harringtonolide involved construction of the five-membered ether ring by means of intramolecular nucleophilic attack on a suitably located cyclopropyl ring with concomitant opening to form the adjacent methyl group (Scheme **1.18**). This ring-opening process had been shown to be feasible in earlier model studies.[43]



66 **1**

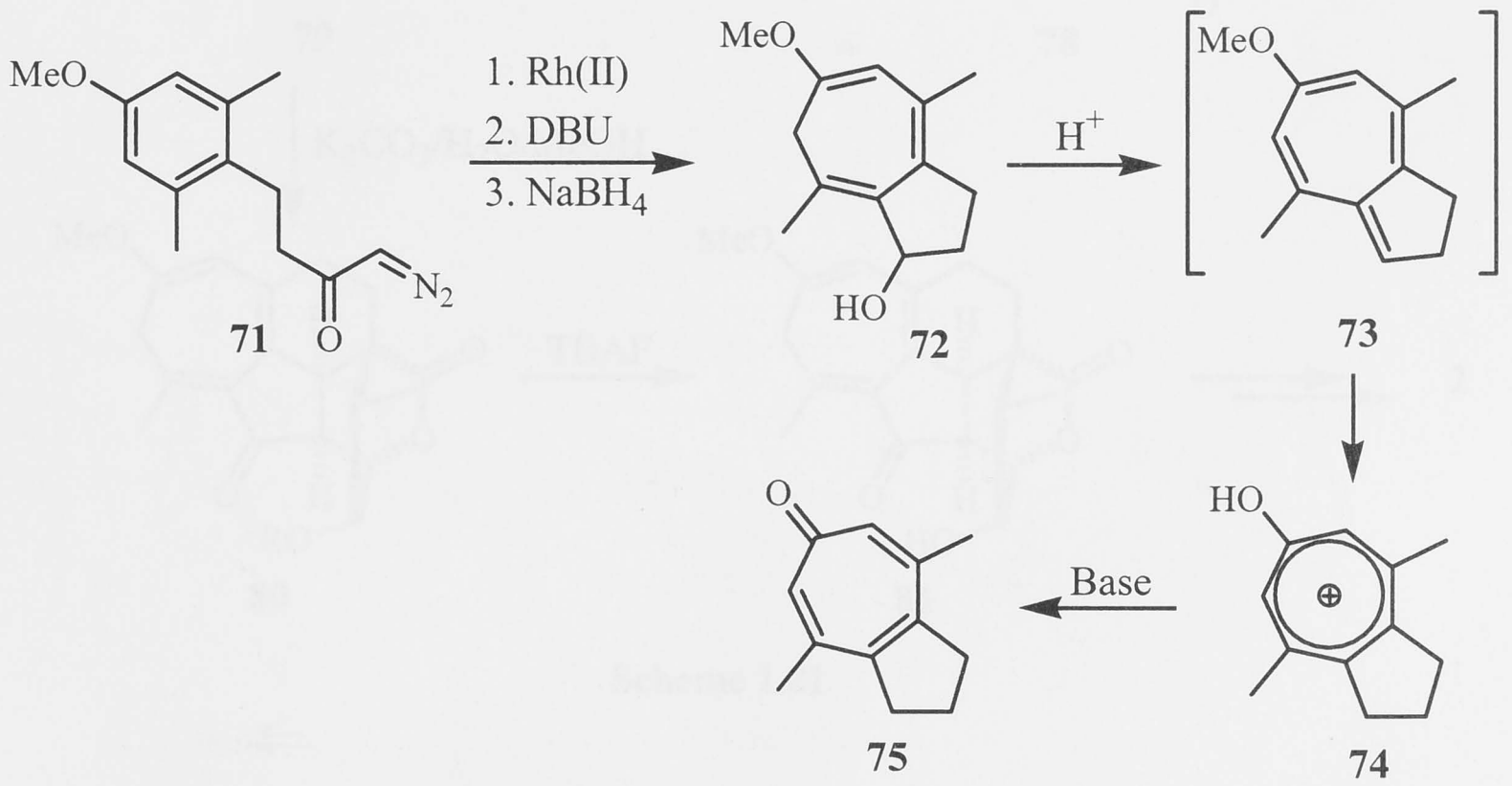
Scheme 1.18

Synthesis of the advanced α-diazocarbonyl intermediate **68** was successful, and arene cyclopropanation again proceeded smoothly in 93% yield (Scheme **1.19**).[44] However, all attempts to invert the stereochemistry at the indanone ring junction in compound **69** led to decomposition products. Attempted removal of the silyl ether protecting group with tetrabutylammonium fluoride also failed.



Scheme 1.19

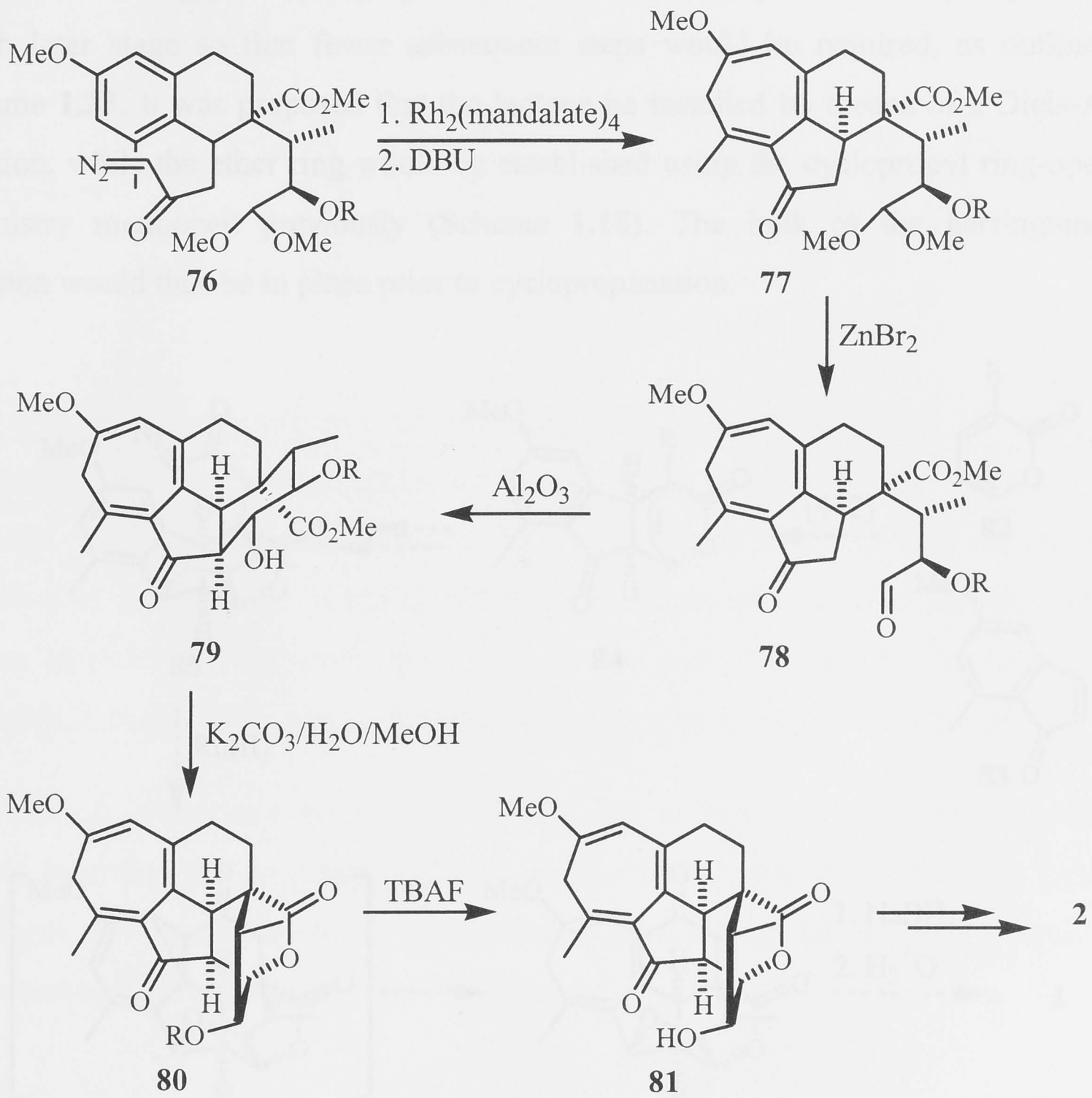
It was then proposed that modifying Scheme **1.14,** by incorporating a hydroxyl adjacent to the acetal function, should ultimately culminate in the synthesis of hainanolidol and thus constitute a formal synthesis of harringtonolide (Scheme **1.1**). Model studies confirmed that ionisation of the allylic hydroxy group with simultaneous formation of the tropone moiety, *via* tropylium ion **74**, was practicable (Scheme **1.20**).



Scheme 1.20

Intermediate **76** (R=TBDMS) was prepared using methodology employed in earlier work, but with the newly incorporated hydroxyl masked as a *tert.*-butyldimethylsilyl ether (Scheme **1.21**).[45] This compound was carried through to lactone **80**, at which point it was discovered that it was not possible to deprotect the alcohol function. This was a direct consequence of the folding of the silyl ether group into a very hindered

environment. When the more labile isopropyldimethylsilyl ether was instead used, treatment of the acetal with zinc bromide furnished the aldehyde in only 20% yield. However, protection with the diethylisopropylsilyl group, led to lactone **80** (R=DEIPS) in good yield. Finally, treatment with tetrabutylammonium fluoride produced the alcohol in 85% yield which, when treated with acid, afforded hainanolidol. The synthesis had thus been completed in a total of 22 steps from benzoic acid.



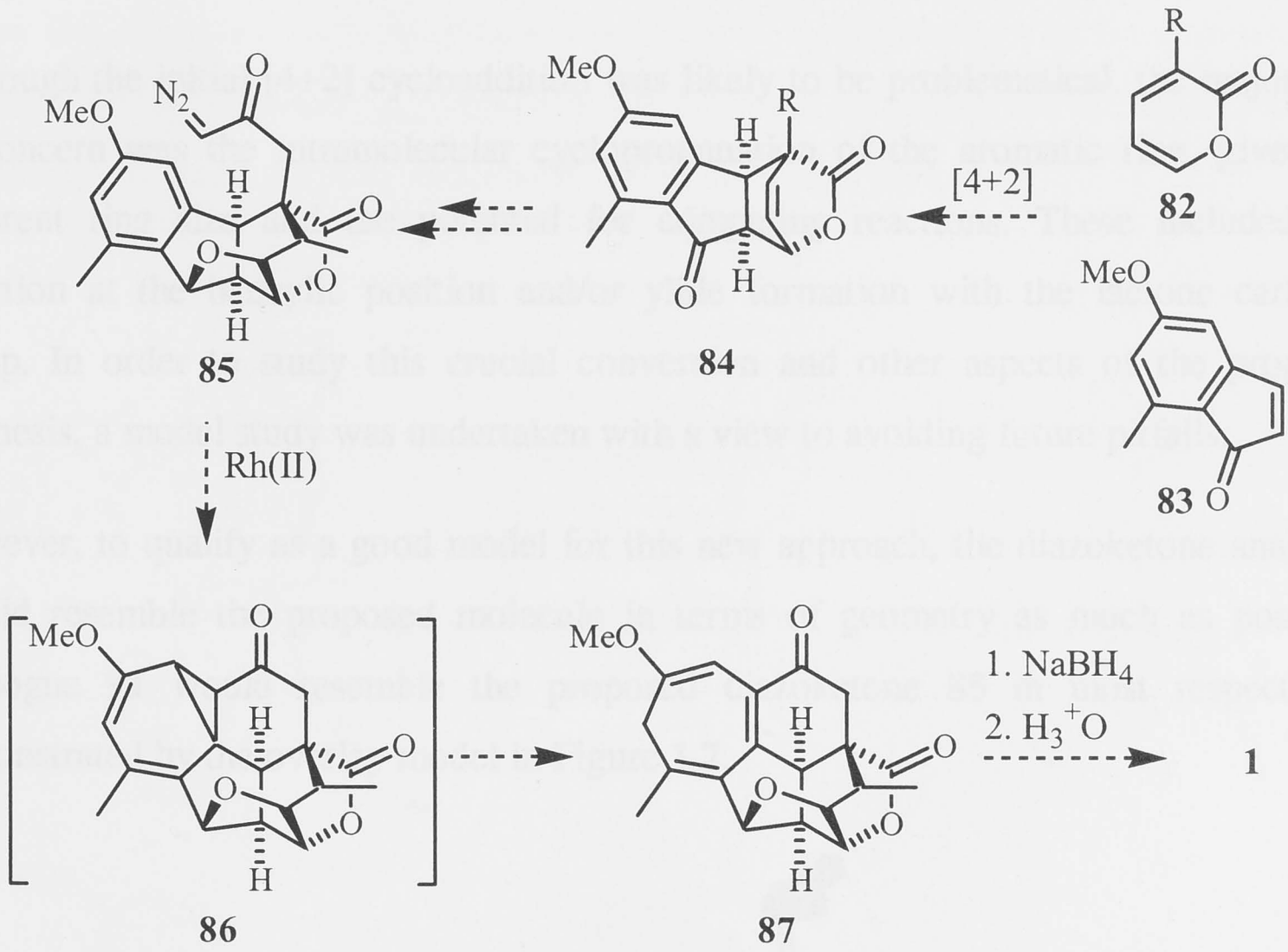
76 **77** **78** **79** **80** **81**

Scheme 1.21

SECTION 1.4 A New Approach

One of the major shortcomings of the strategies detailed above is the relatively early formation of the reactive cycloheptatriene moiety and the need to carry out extensive manipulations in its presence. The resulting difficulties provided the motivation for discovering a new route to harringtonolide.

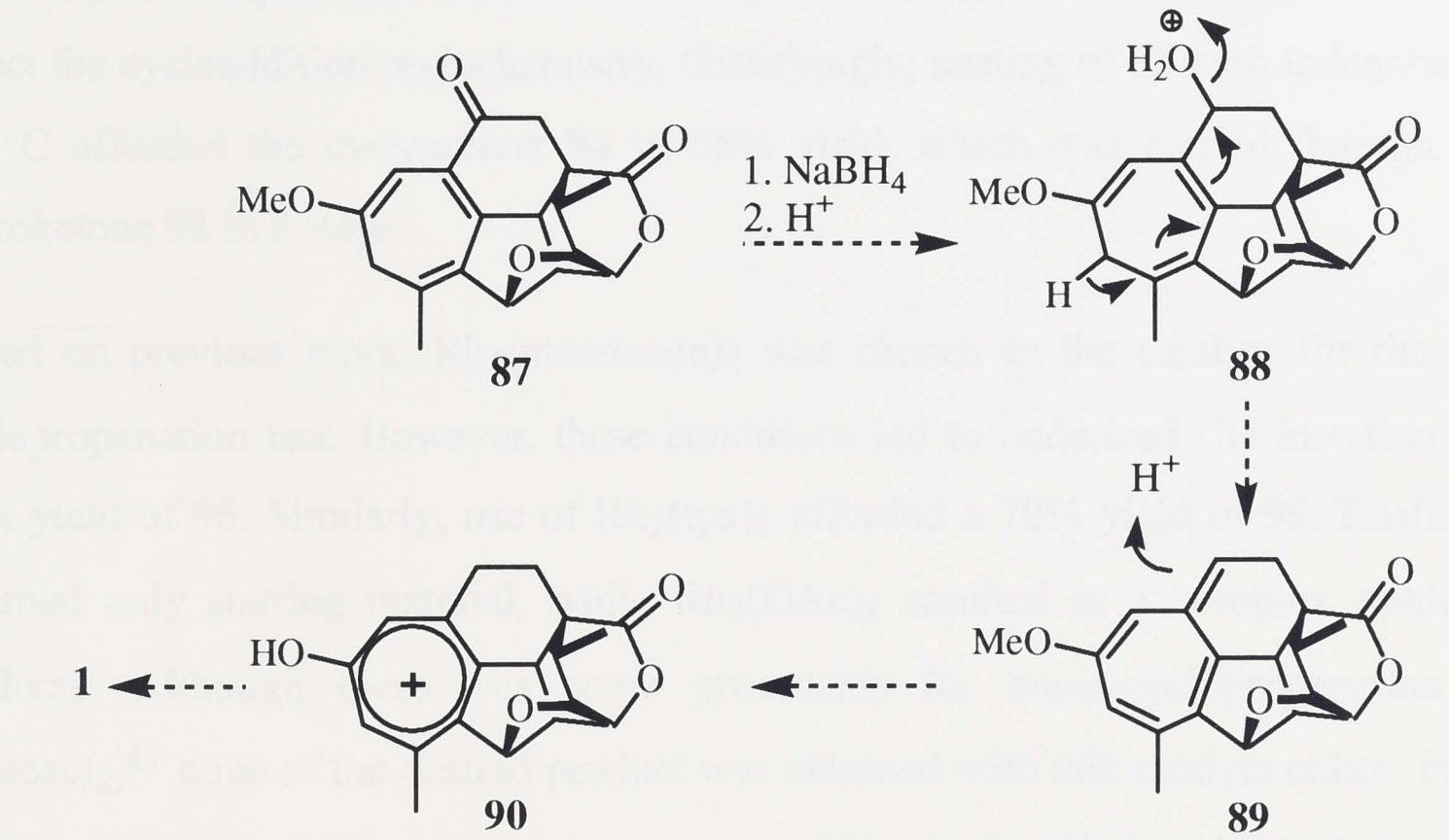
In this new strategy, the cyclopropanation-tautomerisation process would be placed at a much later stage so that fewer subsequent steps would be required, as outlined in Scheme **1.22**. It was proposed that the lactone be installed by means of a Diels-Alder reaction, while the ether ring would be established using the cyclopropyl ring-opening chemistry mentioned previously (Scheme **1.18**). The bulk of the harringtonolide skeleton would thus be in place prior to cyclopropanation.



Scheme 1.22

Attack of the carbenoid on the aromatic ring would generate norcaradiene **86**, followed by rearrangement and conjugation to give **87**. Finally, conversion to **1**, requiring deletion of the benzylic carbonyl and rearrangement to the tropone, would be a one-pot

process and proceed *via* tropylium ion intermediate **90**, which was expected to act as a thermodynamic sink (Scheme **1.23**).



Scheme 1.23

Although the initial [4+2] cycloaddition was likely to be problematical, the major area of concern was the intramolecular cyclopropanation of the aromatic ring, given the different ring size and the potential for competing reactions. These included CH insertion at the benzylic position and/or ylide formation with the lactone carbonyl group. In order to study this crucial conversion and other aspects of the proposed synthesis, a model study was undertaken with a view to avoiding future pitfalls.

However, to qualify as a good model for this new approach, the diazoketone analogue should resemble the proposed molecule in terms of geometry as much as possible. Analogue **91** would resemble the proposed diazoketone **85** in most respects, as demonstrated by the overlay model in Figure **1.7**.

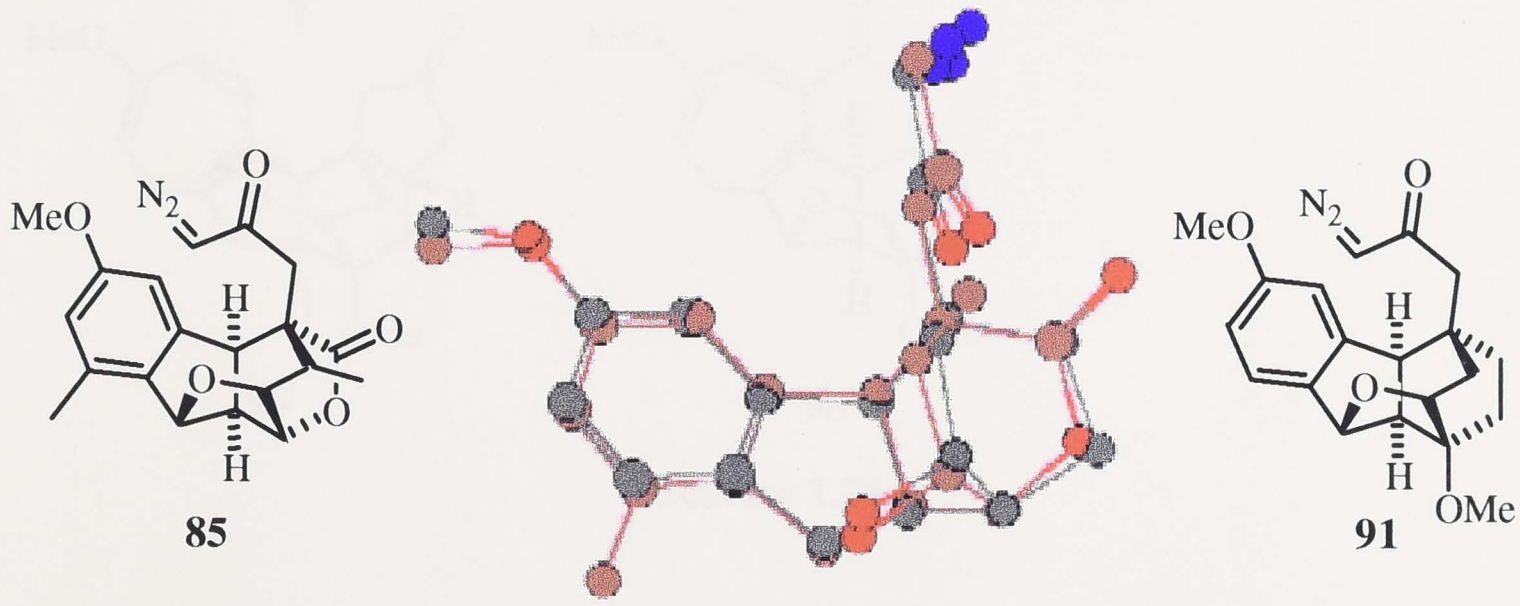
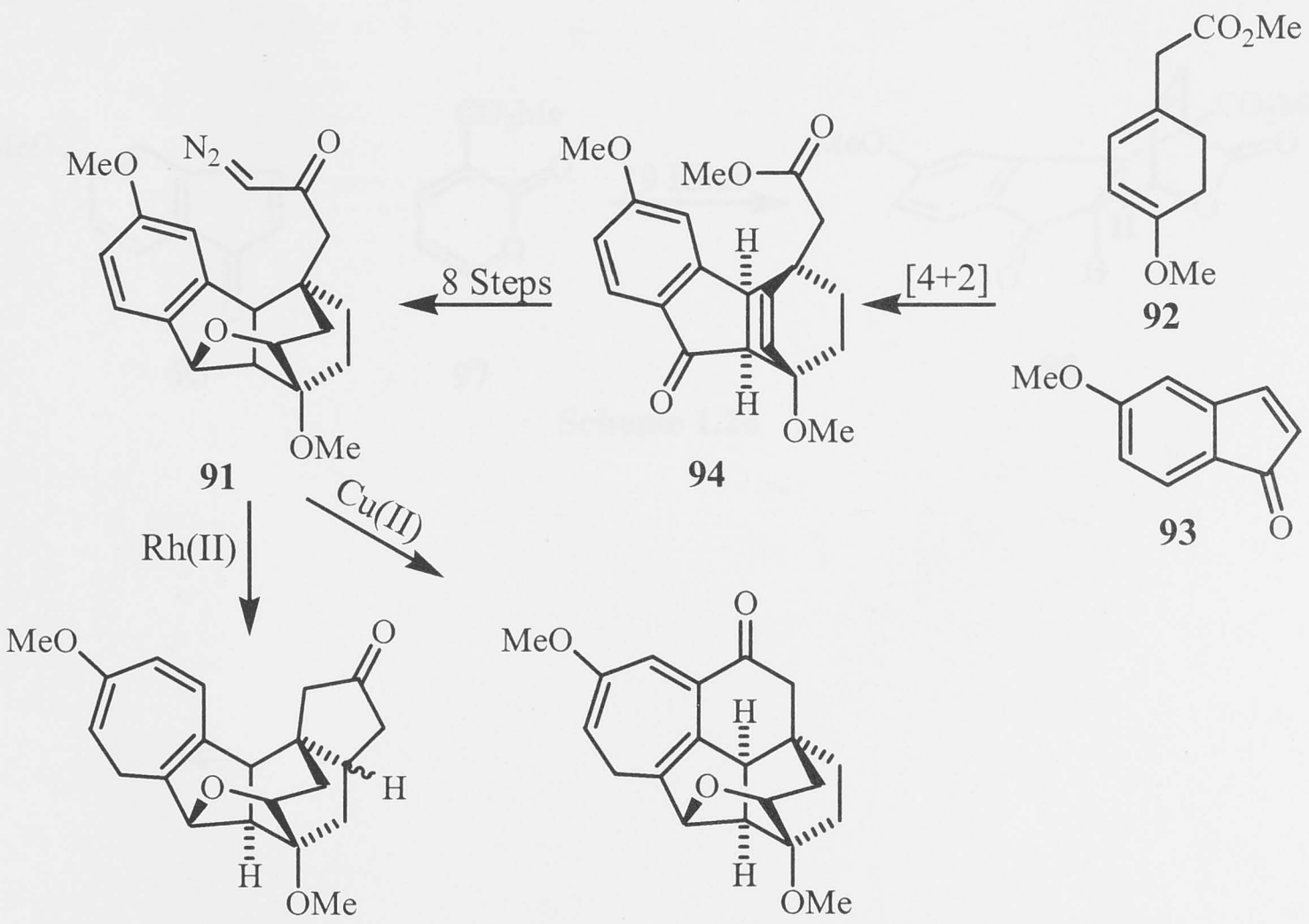


Figure 1.7

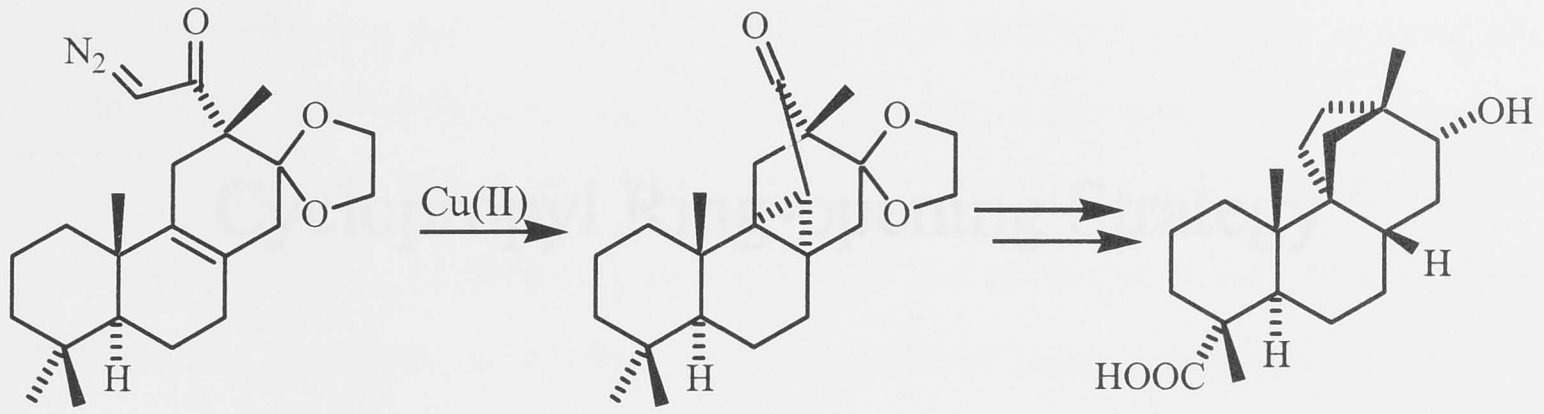
The results from the model study are summarised below (Scheme **1.24**).[46] Indenone **93** was easily prepared from *m*-methoxycinnamic acid in 3 steps, while diene **92** was chosen in the expectation that the methoxyl would provide sufficient activation and direct the cycloaddition regiochemistry. Gratifyingly, heating of **92** with indenone **93** at 125°C afforded the cycloadduct **94** in 56% yield, which was carried through to α-diazoketone **91** in 8 steps.

Based on previous work, $Rh_2(mandelate)_4$ was chosen as the catalyst for the initial cyclopropanation test. However, these conditions led to undesired CH insertion and a 50% yield of **95**. Similarly, use of $Rh_2(tpa)_4$ afforded a 70% yield of **95**. $Rh_2(acam)_4$ returned only starting material, while $Rh_2(OAc)_4$ resulted in a complex mixture of products. Although there was some precedents for arene-cyclopropanation with $Cu(acac)_2$,[47] none of the desired product was obtained with this catalyst either. Finally, **96** was obtained in 30% yield, after treatment of **91** with bis(*N*-*t*-butylsalicylaldiminato) copper (II) and subsequent conjugation with DBU. Disappearance of the characteristic signals from the aromatic ring system in the ^{1}H-NMR spectrum and the appearance of signals at 5.91 and 5.44 ppm, confirmed that **96** had been formed.



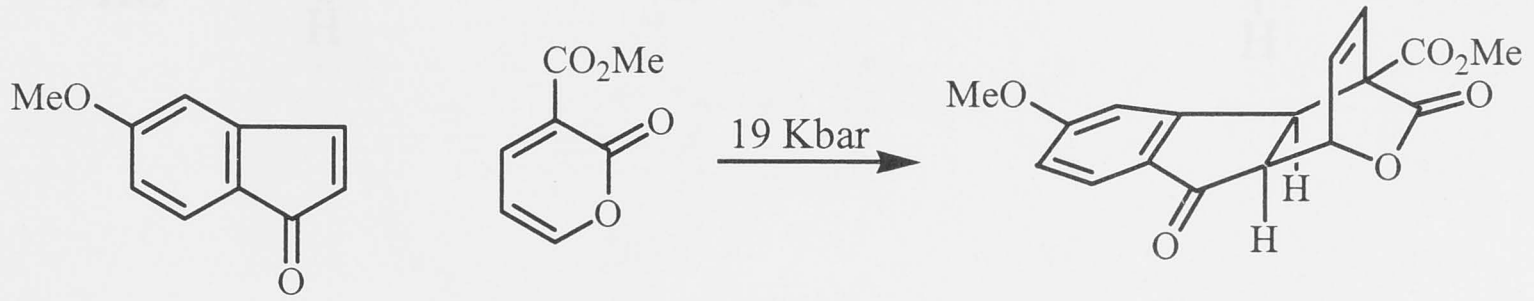
Scheme 1.24

Although the model system demonstrated that geometrical restraints still permitted cyclopropanation to take place, the possibility of ylide formation remained. To avoid this outcome, protection of the lactone carbonyl may be necessary. Zaragozá's synthesis of thrysflorin A methyl ester provides an encouraging precedent (Scheme **1.25**).[48]



Scheme 1.25

At the end of the model study, a Diels-Alder reaction of indenone **93** with pyrone **97** was conducted at high pressure by David Appels (Scheme **1.26**).[46] The adduct **98**, whose structure was secured by X-ray crystallography, was obtained in 50% yield with the required regio- and stereochemistry.

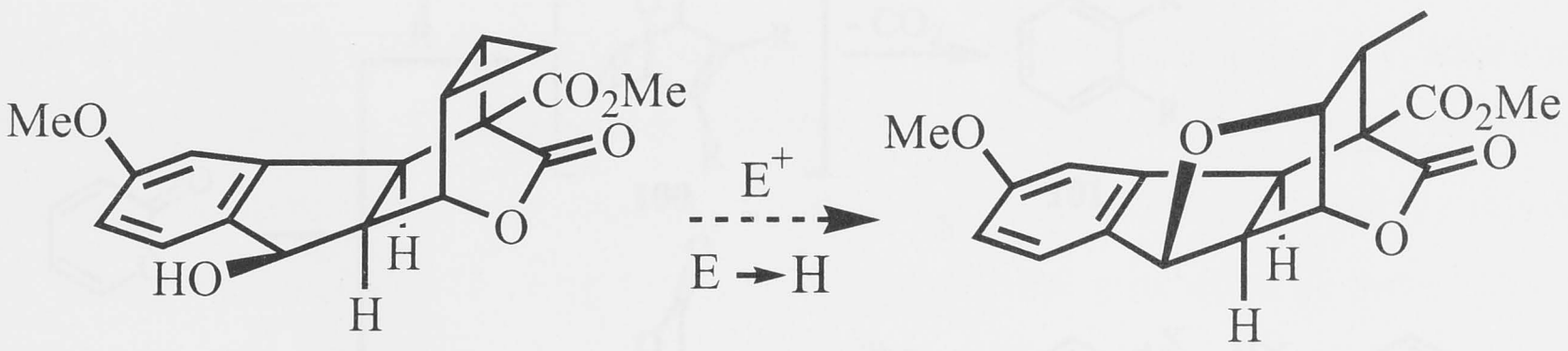


93 **97** **98**

Scheme 1.26

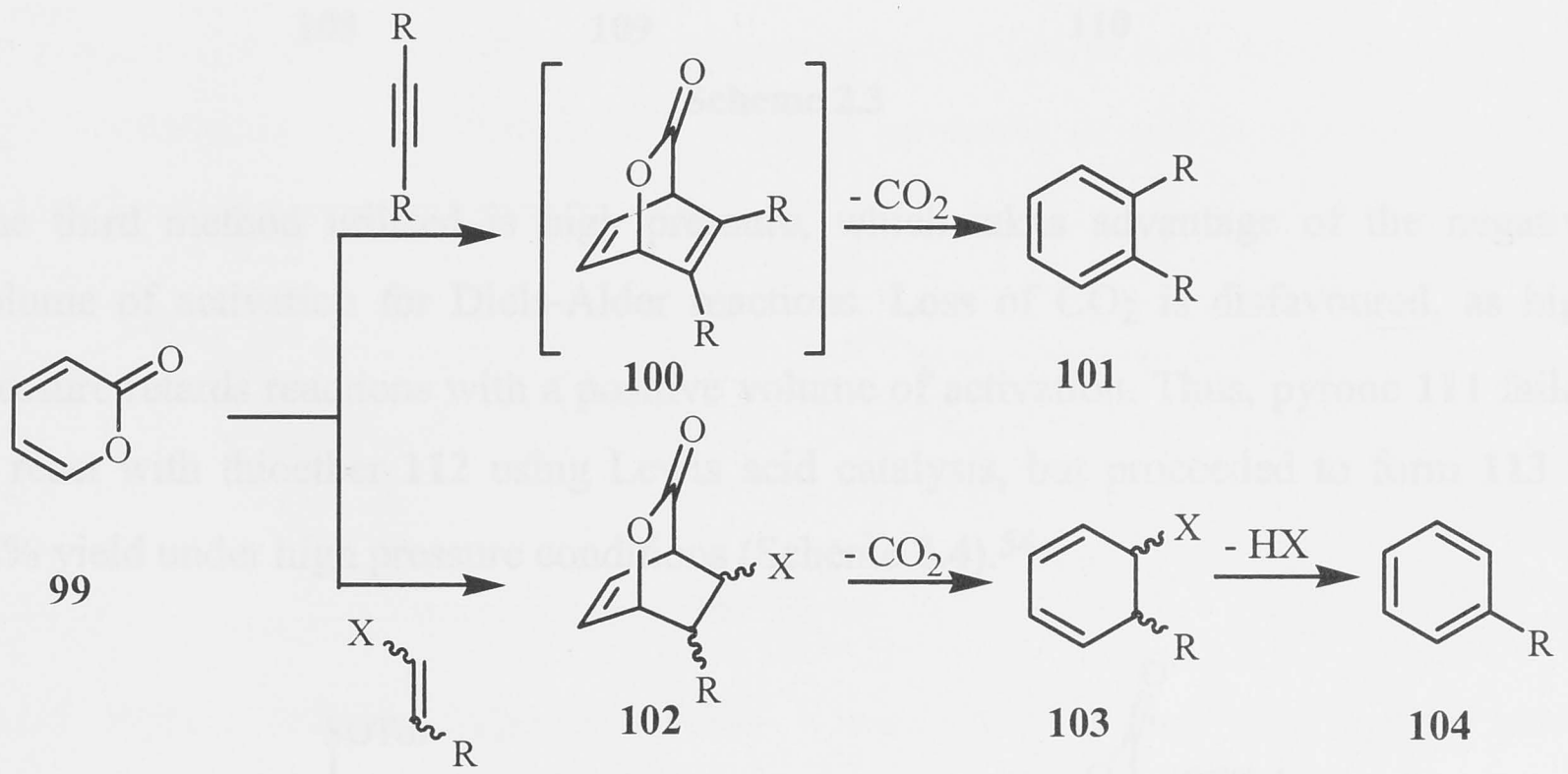
Chapter Two

Cyclopropyl Ring-opening Strategy



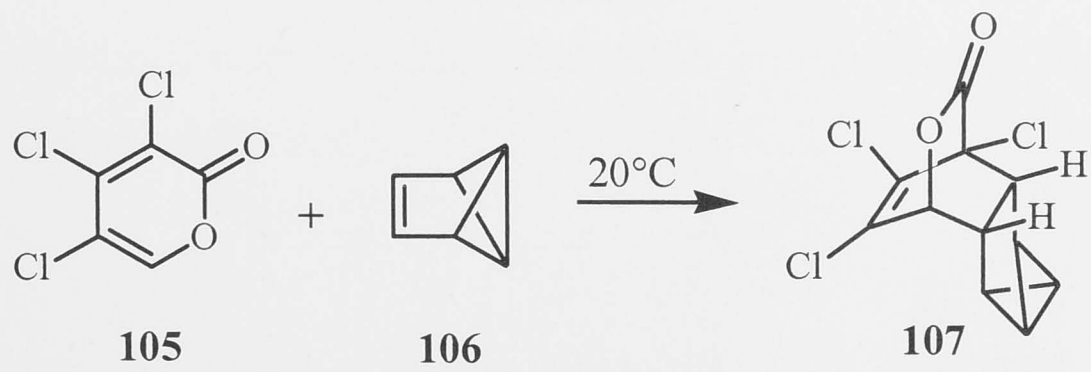
SECTION 2.1 Cycloadditions of Pyrones

Researchers have shown considerable interest in the [4+2] cycloadditions of 2-pyrones over the past three decades and this work has been the subject of several recent reviews.[49,50] 2-pyrones are aromatic in nature, and therefore undergo cycloadditions less readily than most conjugated dienes. Initial work in this area was confined to the synthesis of aromatic products where loss of carbon dioxide leads either to dihydrobenzenes **103** or to aromatic products **104** *via* subsequent loss of HX (Scheme **2.1**).[51] Recently, however, a number of methods have been developed to avoid CO_2 extrusion and are providing chemists with a viable route to the highly functionalised bicyclic lactones **102**.



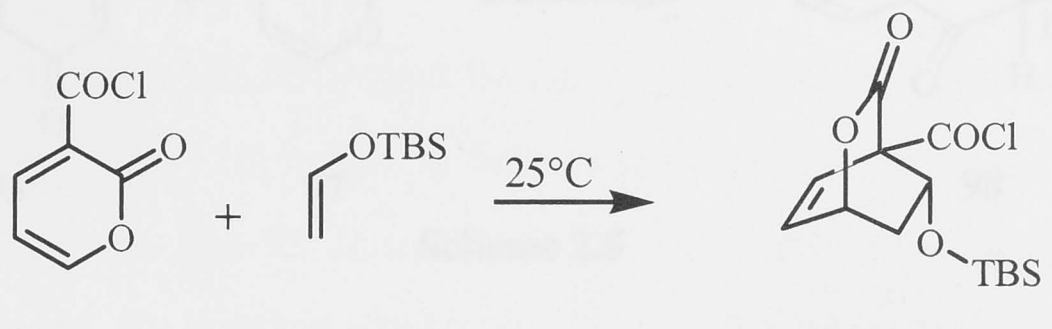
Scheme 2.1

In order to preserve the lactone functionality, three main methods have been introduced to facilitate room temperature cycloadditions.[49] The first method is to impose geometric strain on the diene or the dienophile, which greatly increases their reactivity. For example, the inherent strain in **106** results in reaction with **105** at 20°C to produce **107** in 95% yield (Scheme **2.2**).[52]



Scheme 2.2

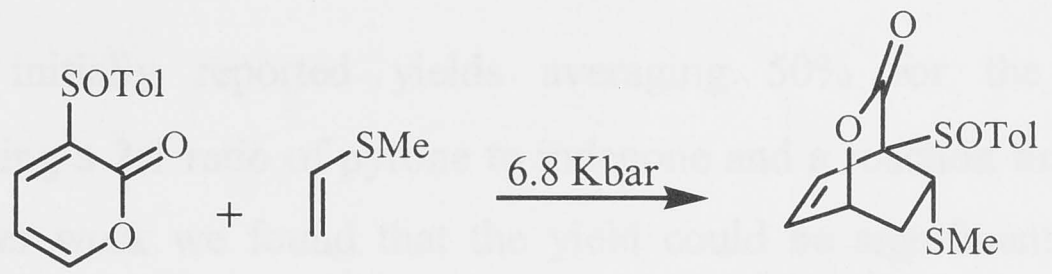
The second method is to match the electronic properties of the diene with those of the dienophile. This may be accomplished by introducing an electron withdrawing group into the 3- or 5-positions of the pyrone and by pairing it with an electron rich dienophile in an inverse-electron-demand Diels-Alder reaction. Thus the extremely electron-poor pyrone, 3-chlorocarbonyl-2-pyrone (**108**), reacts smoothly with dienophile **109** to afford **110** in 77% yield (Scheme **2.3**).[53] Conversely, the introduction of electron donating groups into the 3- or 5-positions facilitates cycloadditions with electron-poor dienophiles.



108 **109** **110**

Scheme 2.3

The third method utilised is high pressure, which takes advantage of the negative volume of activation for Diels-Alder reactions. Loss of CO_2 is disfavoured, as high pressure retards reactions with a positive volume of activation. Thus, pyrone **111** failed to react with thioether **112** using Lewis acid catalysis, but proceeded to form **113** in 98% yield under high pressure conditions (Scheme **2.4**).[54]

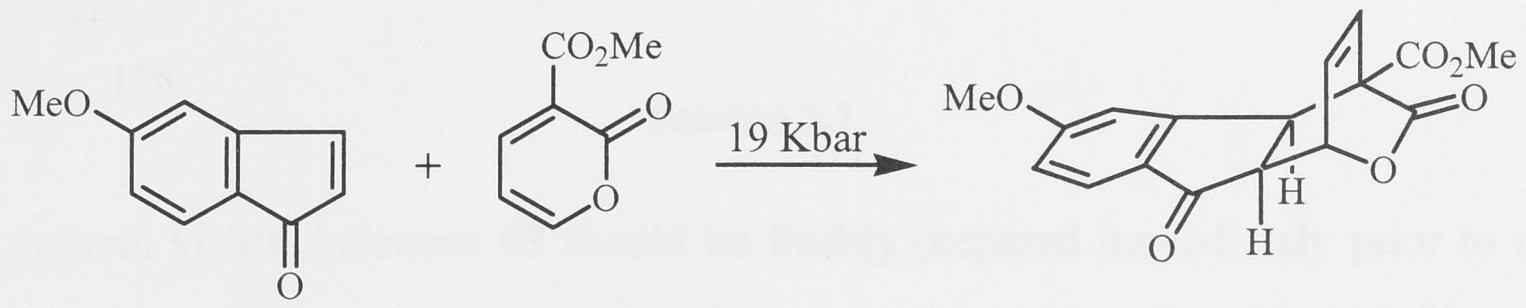


111 **112** **113**

Scheme 2.4

SECTION 2.2 Harringtonolide Framework Construction

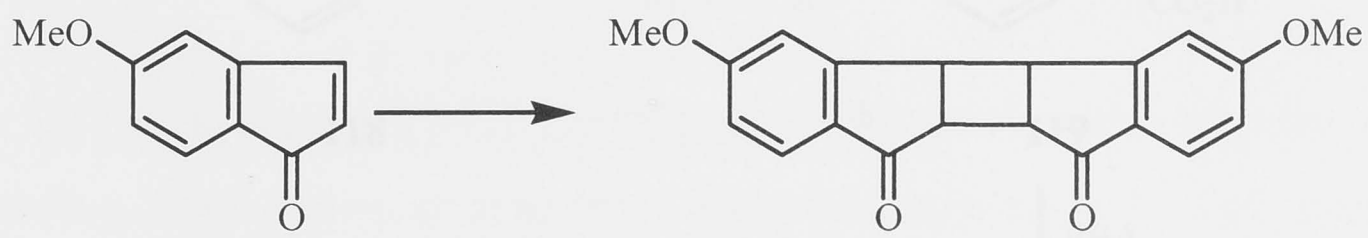
The latter two methods (*i.e.* electron-withdrawing group at the 3-position and high pressure) are employed in providing activation for our key [4+2] cycloaddition reaction (Scheme **2.5**).



93 **97** **98**

Scheme 2.5

No product was obtained when high temperature and Lewis acid catalysis conditions were investigated. In fact, Lewis acid catalysis promotes an undesirable side reaction and the formation of dimer **114** (Scheme **2.6**).

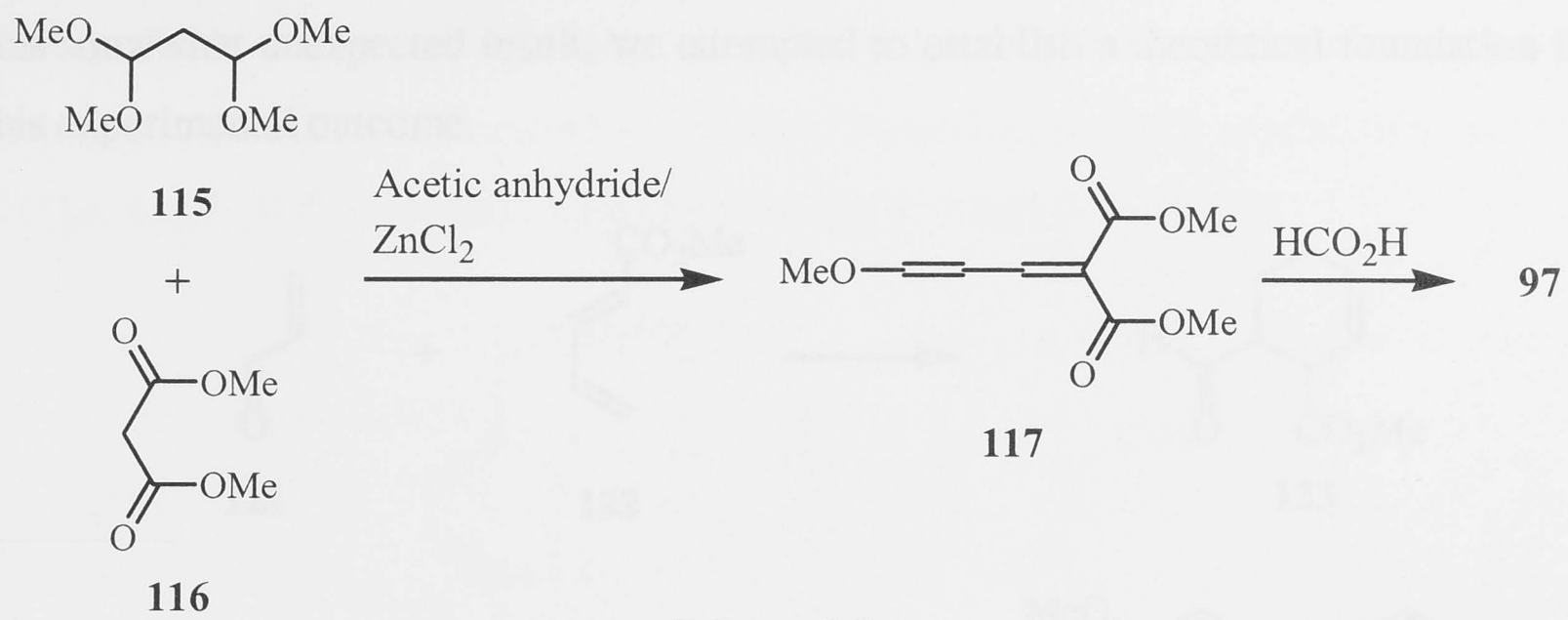


93 **114**

Scheme 2.6

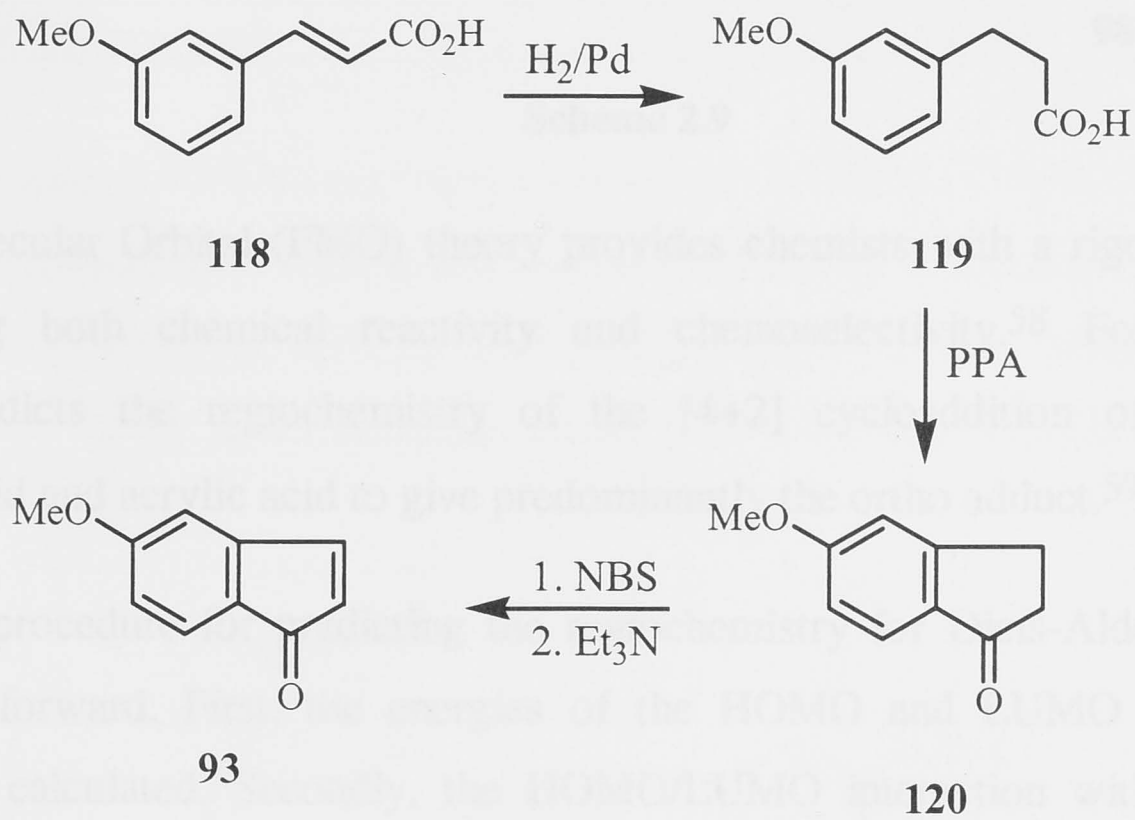
David Appels initially reported yields averaging 50% for the high pressure cycloaddition using a 2:1 ratio of pyrone to indenone and a reaction time of 4 hours.[46] However, in later work we found that the yield could be significantly improved by extending the reaction time. Yields of 70% were typically obtained when the reactants were subjected to 19 Kbar for 24 hours. Reaction times of longer than 24 hours did not result in higher yields.

It was also discovered that the amount of pyrone **97**, which can be sourced commercially or synthesised from bis(dimethyl acetal) **115** on a 10 g scale (Scheme **2.7**),[55] could be reduced with no detrimental effect of yields, such that a 1:1 ratio of diene to dienophile was sufficient.



Scheme 2.7

For optimal yields, indenone **93** should be freshly prepared immediately prior to each reaction. While indanone **120**, prepared from *m*-methoxycinnamic acid (**118**),[56] can be stored indefinitely, indenone **93** dimerises rapidly at room temperature, especially on exposure to sunlight. Even when stored at –20°C, pure **93** is not stable, although in dilute solutions it can be stored for short periods of time.

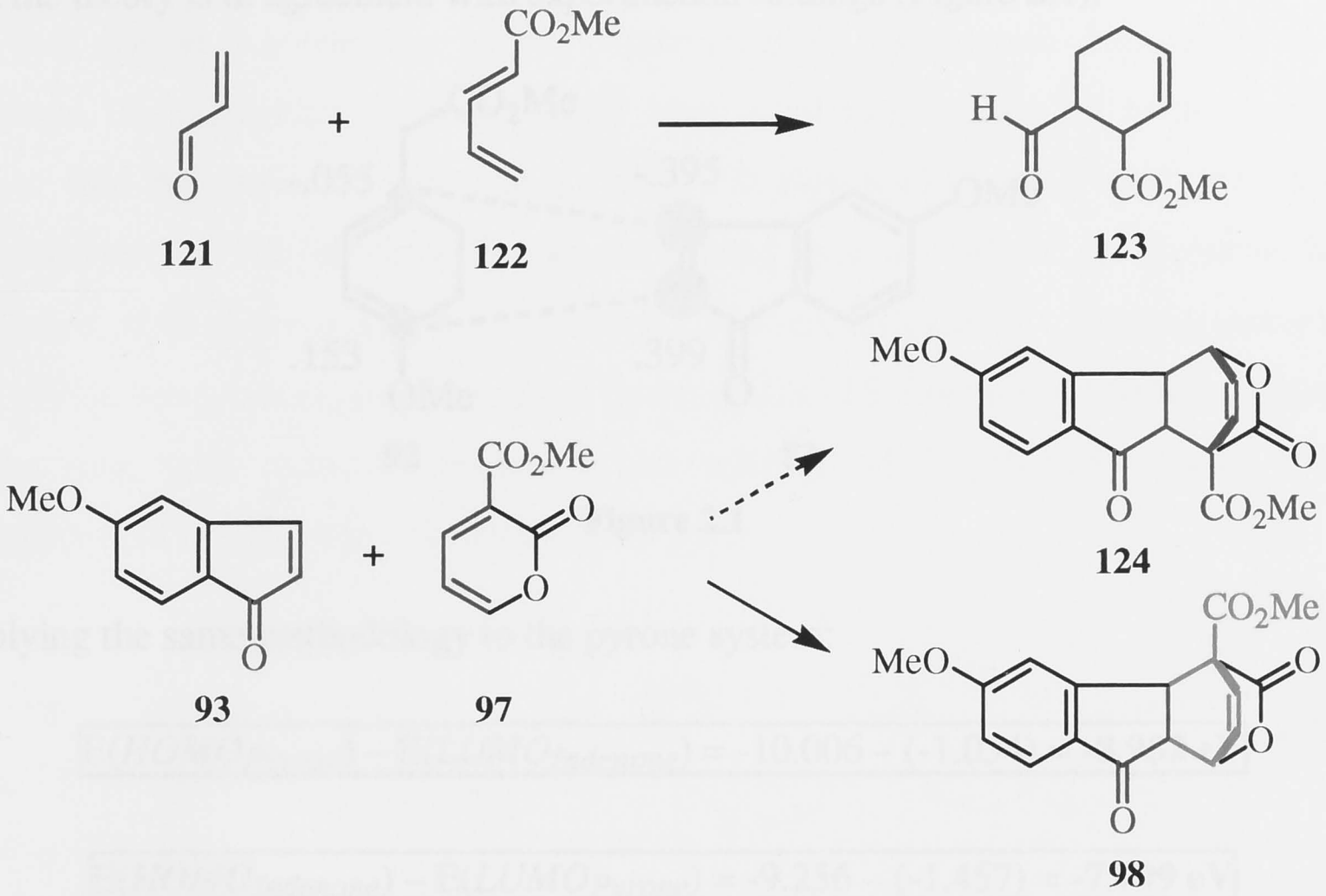


Scheme 2.8

SECTION 2.3 Frontier Orbital Calculations

The regiochemistry observed in the cycloaddition reaction is particularly interesting. In fact, based on earlier precedent, it is entirely contrary to that which would be predicted from qualitative considerations (Scheme **2.9**). None of the alternate regioisomer **124** is formed, even though it is analogous to the formation of **123**, a known reaction.[57] Given

this somewhat unexpected result, we attempted to establish a theoretical foundation for this experimental outcome.



Scheme 2.9

Frontier Molecular Orbital (FMO) theory provides chemists with a rigorous basis for understanding both chemical reactivity and chemoselectivity.[58] For example, it correctly predicts the regiochemistry of the [4+2] cycloaddition of butadiene-1-carboxylic acid and acrylic acid to give predominantly the ortho adduct.[59]

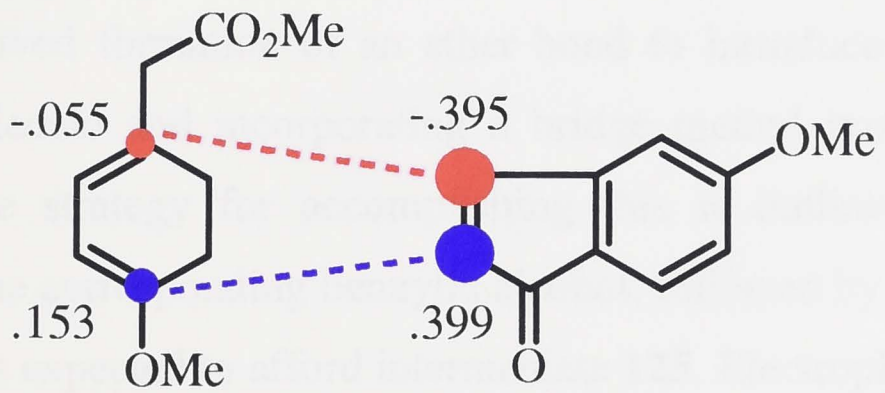
The general procedure for predicting the regiochemistry for Diels-Alder reactions is quite straightforward. First, the energies of the HOMO and LUMO states for the reactants are calculated. Secondly, the HOMO/LUMO interaction with the smallest energy gap (*i.e.* the most favourable interaction) is determined. The FMO coefficients can now be found by examining the molecular orbitals for the above interaction. Finally, the coefficients are matched according to sign and size.

Examining the model system of **92** and **93**, we find the following:

$$E(HOMO_{Diene}) - E(LUMO_{Dienophile}) = -8.773 - (-1.054) = \mathbf{-7.719\ eV}$$

$$E(HOMO_{Dienophile}) - E(LUMO_{Diene}) = -9.256 - (-0.127) = \mathbf{-9.128\ eV}$$

Clearly, the $HOMO_{Diene}/LUMO_{Dienophile}$ interaction is favoured, in accordance with a normal-electron-demand Diels-Alder reaction. Matching the FMO coefficients[†], we find that the theory is in agreement with experimental findings (Figure **2.1**).



92 **83**

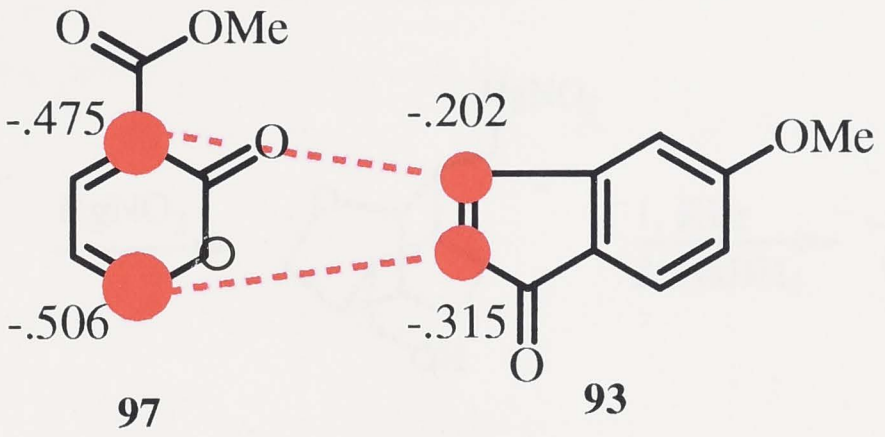
Figure 2.1

Applying the same methodology to the pyrone system:

$$\boxed{E(HOMO_{Pyrone}) - E(LUMO_{Indenone}) = -10.006 - (-1.054) = \mathbf{-8.952\ eV}}$$

$$\boxed{E(HOMO_{Indenone}) - E(LUMO_{Pyrone}) = -9.256 - (-1.457) = \mathbf{-7.799\ eV}}$$

The $HOMO_{Indenone}/LUMO_{Pyrone}$ interaction is now favoured. This is characteristic of an inverse-electron-demand Diels-Alder reaction and can be accounted for by the effect of the electron-withdrawing carboxy ester group in the 3-position. Matching the FMO coefficients, the theory again correctly predicts the observed regiochemistry (Figure **2.2**).



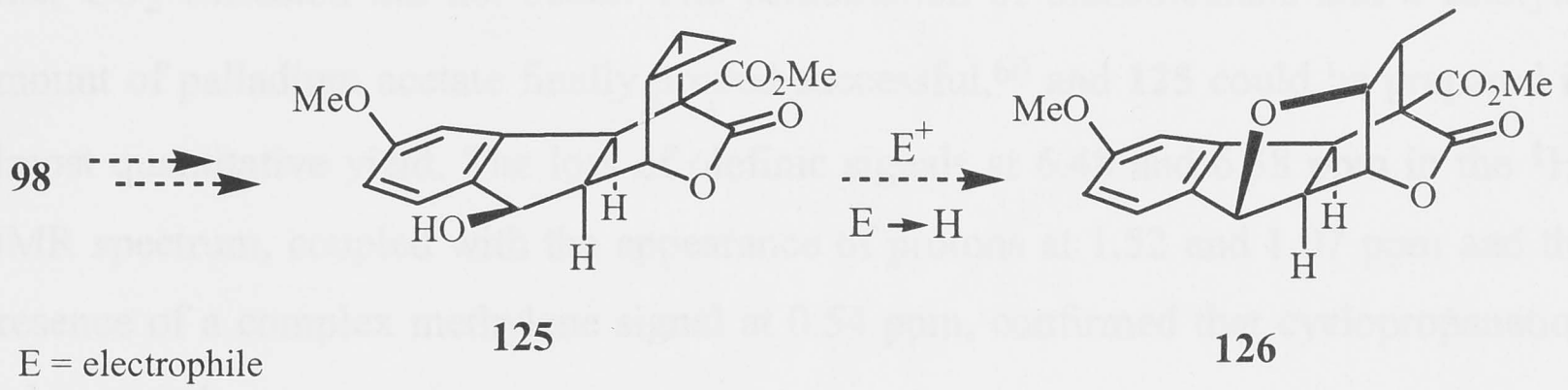
97 **93**

Figure 2.2

[†] Frontier Molecular Orbital calculations were performed on the Spartan (v5.0.1) program with the RHF/PM3 model.

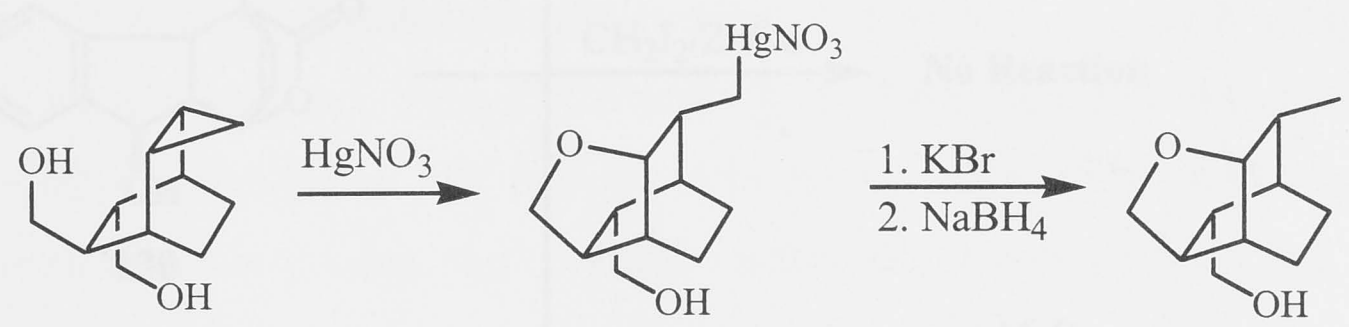
SECTION 2.4 Cyclopropyl Ring-opening Attempts

We next turned our attention to the construction of the internal framework of the molecule. This involved formation of an ether bond to introduce the tetrahydrofuran moiety into the molecule and incorporating a bridge methyl group with the correct stereochemistry. The strategy for accomplishing this is outlined in Scheme **2.10**. Reduction of **98** to the corresponding benzylic alcohol, followed by cyclopropanation of the olefinic bond was expected to afford intermediate **125**. Electrophile induced opening of the ring, with concerted intramolecular addition of the hydroxy group, would hopefully lead to **126** after appropriate work up.



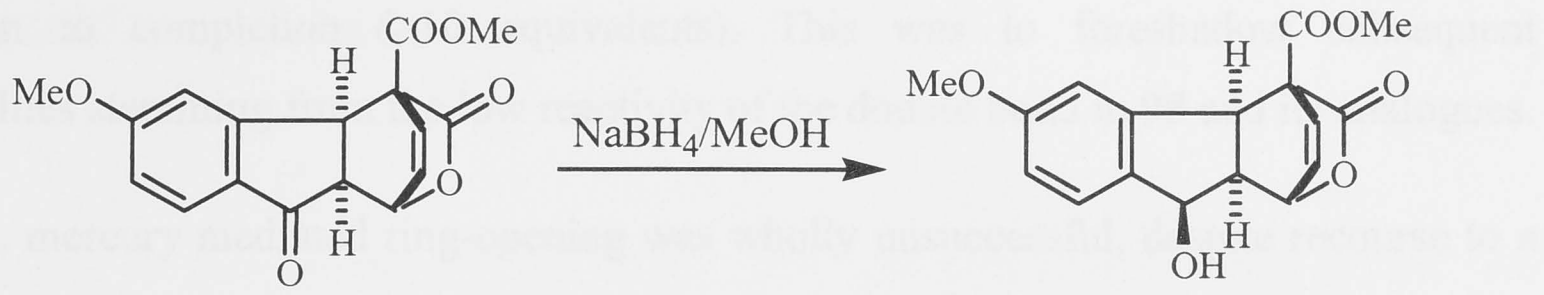
Scheme 2.10

As it was not clear from literature precedents whether the conversion of **125** to **126** would be successful, a model study had been undertaken.[43] With $Hg(NO_3)_3$ as the initiating electrophile, **127** underwent cyclisation to **128** smoothly. Formation of the bromide, followed by sodium borohydride reduction afforded **129** in 80% overall yield.



Scheme 2.11

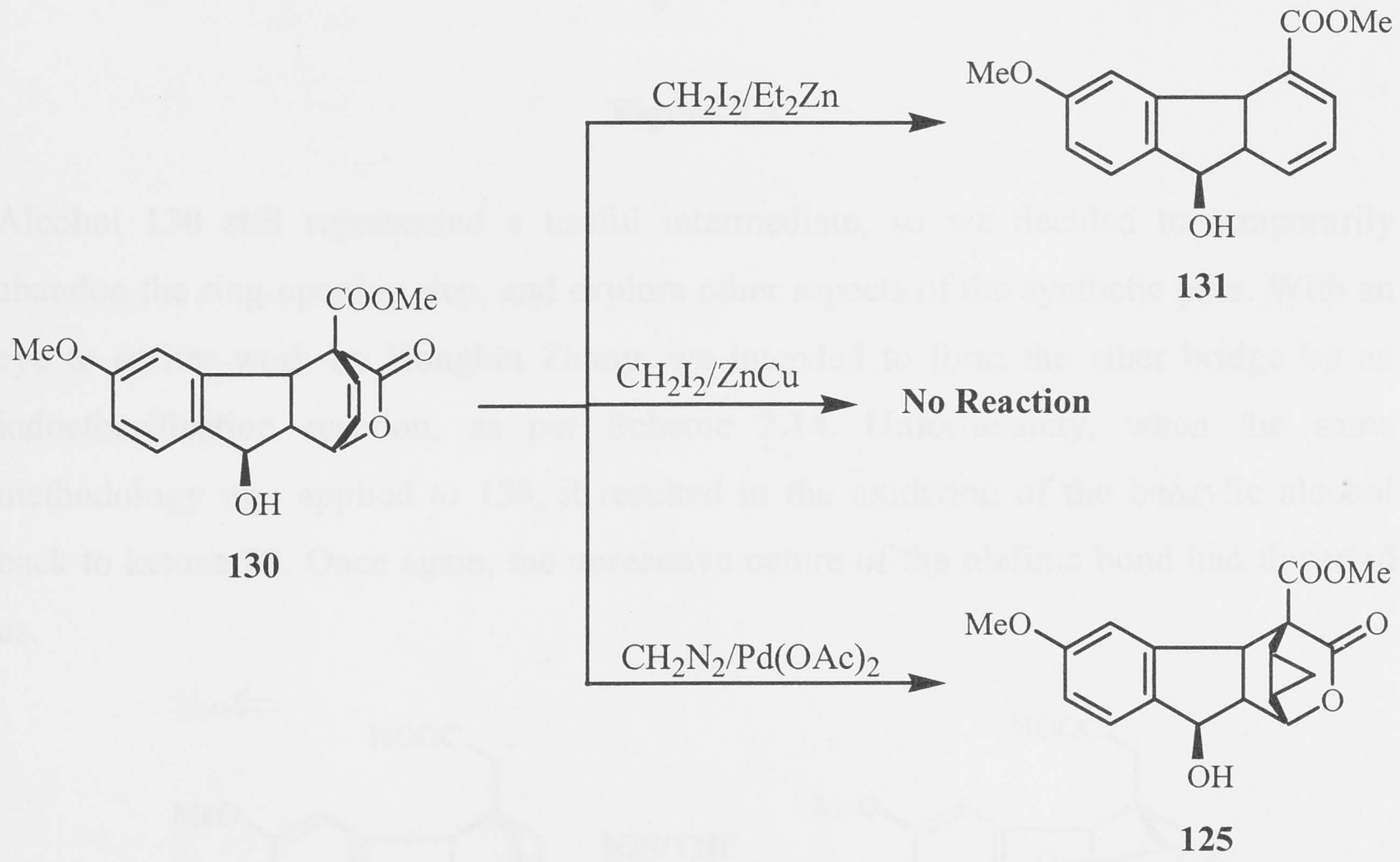
Ketone **98** was reduced to **130** in 77% yield with sodium borohydride in methanol (Scheme **2.12**). The fact that only one diastereomeric alcohol was observed can be ascribed to the concave nature of the upper face of **98** and approach of the hydride from the less hindered side of the molecule.



98 **130**

Scheme 2.12

In an attempt to introduce the cyclopropyl ring, we initially explored Simmons-Smith conditions, but were disappointed to recover only starting material. Diethyl zinc, a more active species, is often used when an electron-poor olefinic bond is present. However, heating at 80°C in benzene merely led to decarboxylation and formation of diene **131**. Surprisingly, when **130** was subjected to the same conditions in the absence of diethyl zinc, CO_2 extrusion did not occur. The combination of diazomethane and a catalytic amount of palladium acetate finally proved successful,[60] and **125** could be prepared in almost quantitative yield. The loss of olefinic signals at 6.48 and 6.38 ppm in the ^{1}H-NMR spectrum, coupled with the appearance of protons at 1.52 and 1.07 ppm and the presence of a complex methylene signal at 0.54 ppm, confirmed that cyclopropanation had occurred.



130 **131** **125**

Scheme 2.13

The formation of a black metallic precipitate on addition of diazomethane, suggested reduction of Pd(II) to Pd(0), so it is unclear which is the actual catalytic species. Of greater concern, however, was the large excess of diazomethane required to force the

reaction to completion (>10 equivalents). This was to foreshadow subsequent difficulties stemming from the low reactivity of the double bond in **98** and its analogues.

Indeed, mercury mediated ring-opening was wholly unsuccessful, despite recourse to a wide range of reagents and conditions. At no time was there any evidence of formation of the desired product – invariably either **125** was recovered or the starting material was completely destroyed. This lack of success led us to surmise that cyclopropanation had taken place on the wrong face of the alkene bond, but X-ray analysis of **125** showed that cyclopropanation had occurred on the *exo* face of the double bond, thus disproving this hypothesis (Figure **2.3**).

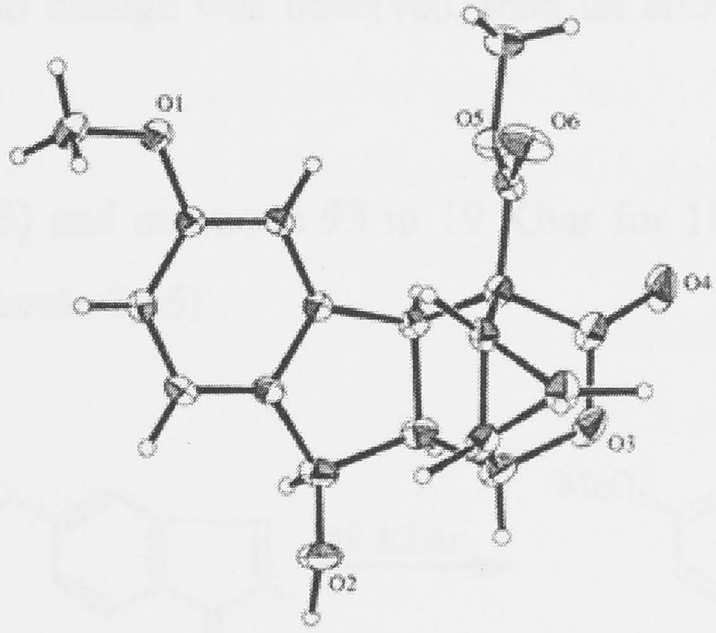
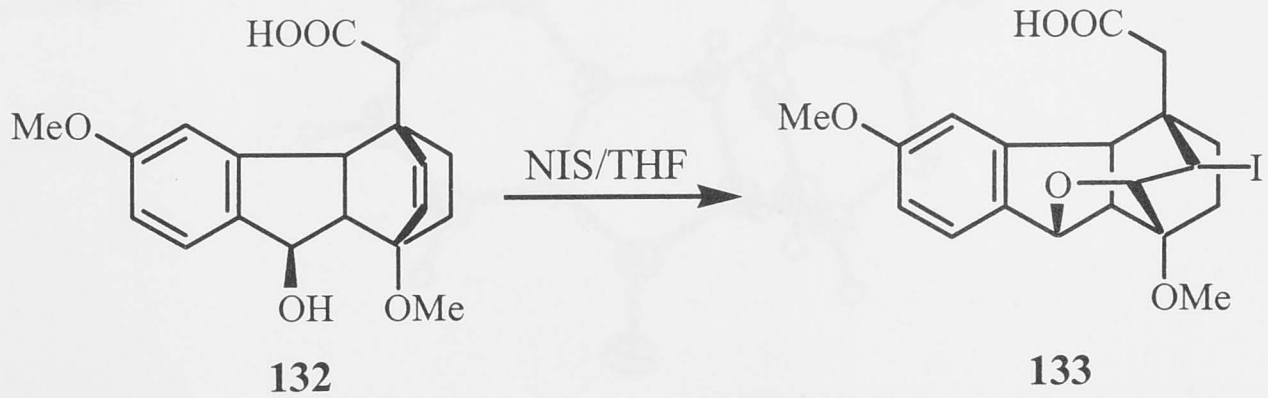


Figure 2.3

Alcohol **130** still represented a useful intermediate, so we decided to temporarily abandon the ring-opening step, and explore other aspects of the synthetic plan. With an eye to earlier work by Hongbin Zhang, we intended to form the ether bridge by an iodoetherification reaction, as per Scheme **2.14**. Unfortunately, when the same methodology was applied to **130**, it resulted in the oxidation of the benzylic alcohol back to ketone **98**. Once again, the unreactive nature of the olefinic bond had thwarted us.



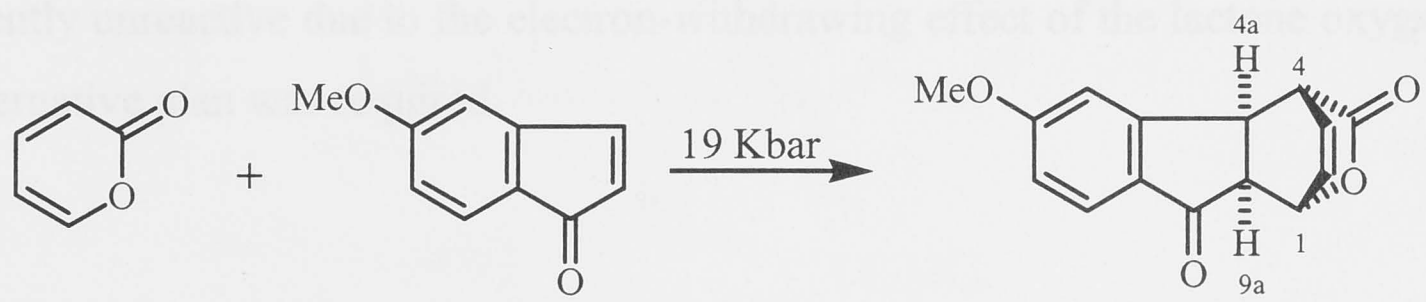
132 **133**

Scheme 2.14

SECTION 2.5 α-Pyrone Cycloadduct : Reactivity

Presumably, the lactone oxygens, the carboxy ester group or a combination of both was responsible for the electron-poor nature of the double bond in **130** and our inability to affect a cyclopropyl ring-opening in **125**. With that in mind, a study was undertaken to probe the reason for the lack of reactivity of the alkene bond. By removing the carboxy ester functionality, it would be possible to discern whether or not it had an influence on the system's reactivity. If an increase in reactivity was observed, then a homologation of the ester prior to the cyclopropanation/ring-opening sequence, might help us surmount previous difficulties. If no change was observed, then an entirely new route would be required.

Subjecting α-pyrone (**133**) and indenone **93** to 19 Kbar for 18 hours afforded a major product in 43% yield (Scheme **2.15**).



133 **93** **134**

Scheme 2.15

A 5.0 Hz coupling between H-1 and H-9a and a 5.9 Hz coupling between H-4 and H-4a suggested regioisomer **134**. The regiochemistry and stereochemistry (*endo*) were confirmed by X-ray analysis (Figure **2.4**).

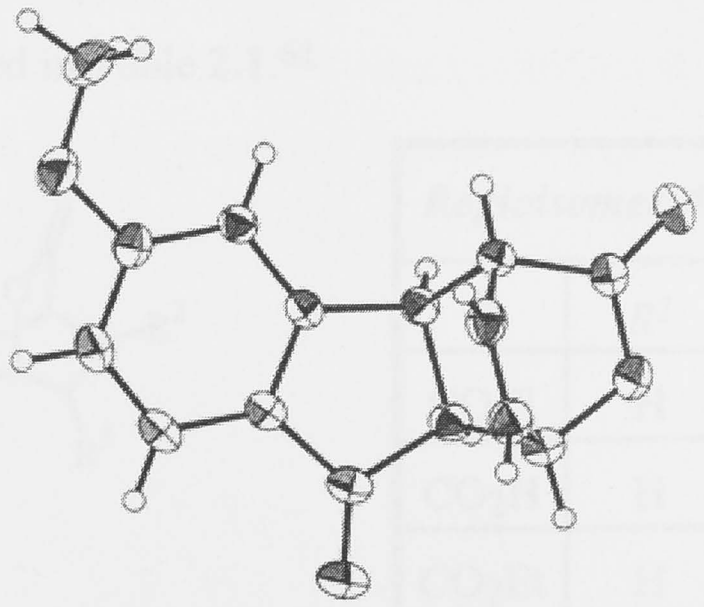
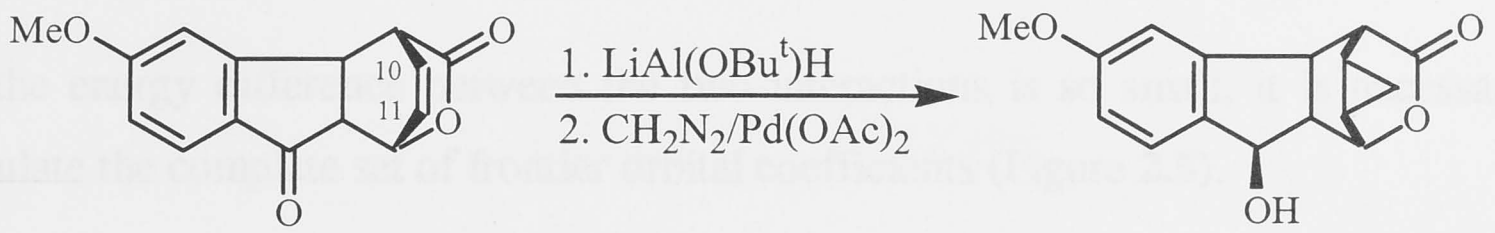


Figure 2.4

Further examination of the ^{1}H-NMR spectrum showed that the absence of a carboxy ester group had little effect on H-11, which had a chemical shift of 6.34 ppm as compared to 6.35 ppm in cycloadduct **98**. A more significant change was noted for H-10, which now appeared at 6.03 ppm, representing an upfield shift of 0.32 ppm.



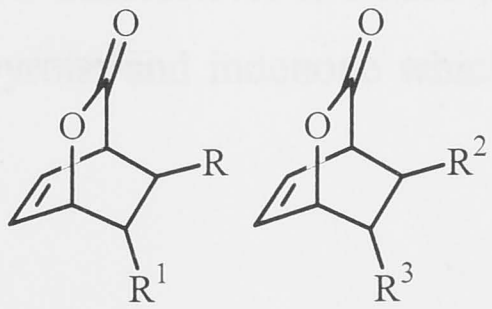
134 **135**

Scheme 2.16

Reduction of **134** with lithium tri(*tert.*-butoxy)aluminum hydride afforded the benzylic alcohol in 73% yield, then cyclopropanation of the olefinic bond was accomplished with diazomethane and palladium acetate, although as before, a large excess of diazomethane was necessary. Subsequent efforts to effect ring-opening of cyclopropyl product **135** failed outright. This result led us to the unhappy conclusion that the system was inherently unreactive due to the electron-withdrawing effect of the lactone oxygens and an alternative plan was required.

SECTION 2.6 α-Pyrone Cycloadduct : Regiochemistry

The high regiochemistry displayed in Scheme **2.15** was completely unexpected – at best we had hoped for a 1:1 ratio of regioisomers. Literature precedent strongly suggested that the absence of an electron-withdrawing group in the 3-position would result in the formation of a mixture of products. Some of the results from a detailed study by Plieninger are summarised in Table **2.1**.[61]



Regioisomer A		***Regioisomer B***		***Ratio A:B***
R	*R^1*	*R^2*	*R^3*	
COCl	H	H	COCl	1:1
CO_2H	H	H	CO_2H	1:1
CO_2Et	H	H	CO_2Et	2:1

Table 2.1

However, frontier molecular orbital theory can help us interpret this result:

$$\boxed{E(HOMO_{Pyrone}) - E(LUMO_{Indenone}) = -9.641 - (-1.054) = \mathbf{-8.587\ eV}}$$

$$\boxed{E(HOMO_{Indenone}) - E(LUMO_{Pyrone}) = -9.256 - (-0.691) = \mathbf{-8.565\ eV}}$$

As the energy difference between the two interactions is so small, it is necessary to calculate the complete set of frontier orbital coefficients (Figure **2.5**).

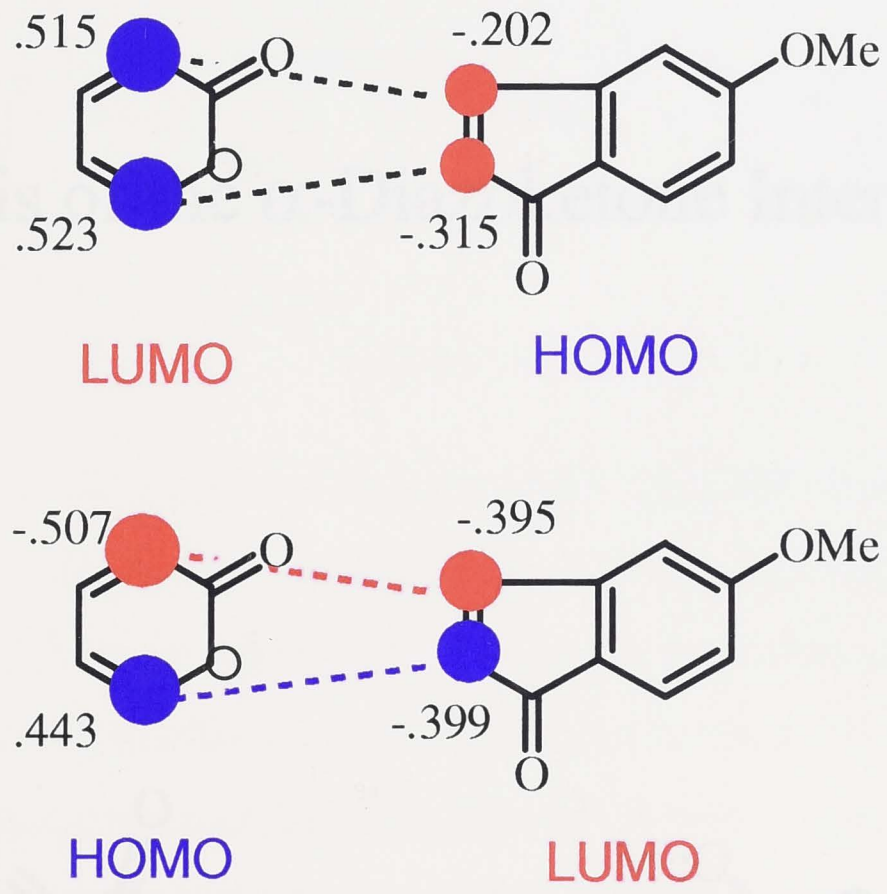
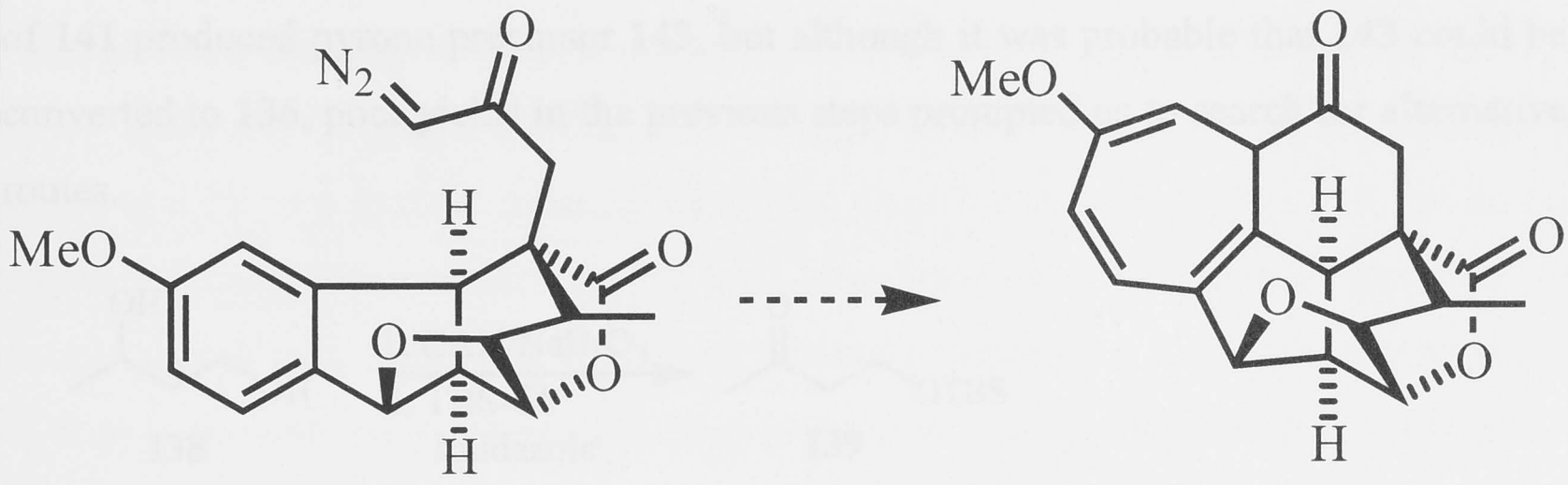


Figure 2.5

The $LUMO_{Pyrone}/HOMO_{Indenone}$ interaction is clearly forbidden, as the signs of the coefficients cannot be matched. By contrast, the $HOMO_{Pyrone}/LUMO_{Indenone}$ interaction is allowed and corresponds to the regiochemistry observed experimentally. In practice, it is found that unsubstituted 2-pyrones are nucleophilic dienes and undergo normal-electron-demand type Diels-Alder reactions. Generally, the directing atom is the endocyclic oxygen and its weak electron-donating power makes the cyclisation unselective. It would therefore appear, that it is the unique combination of both α-pyrone and indenone which provides the unusually high regioselectivity in this reaction.

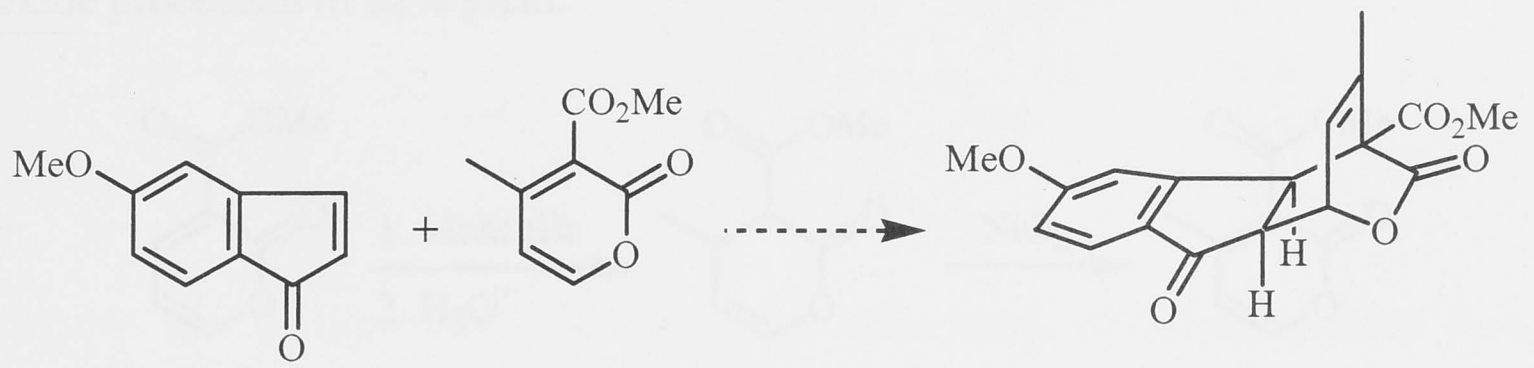
Chapter Three

Synthesis of the α-Diazoketone Intermediate



SECTION 3.1 4-Methyl Pyrone Syntheses

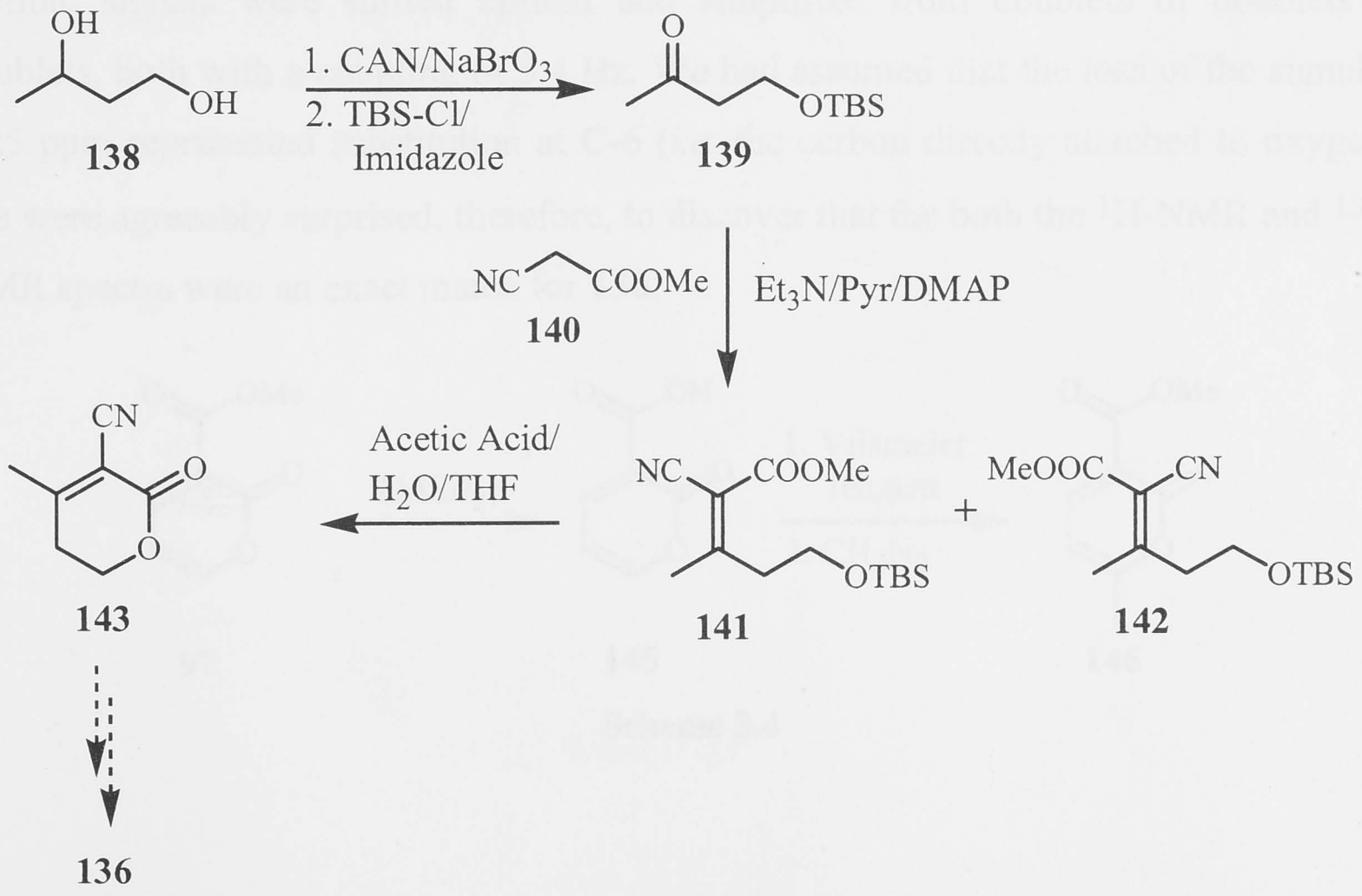
Our next goal was to form pyrone **136** with a methyl group in the 4-position, removing the need to introduce and open the cyclopropyl ring while enhancing the reactivity of the alkene bond in **137** towards electrophiles (Scheme **3.1**).



93 **136** **137**

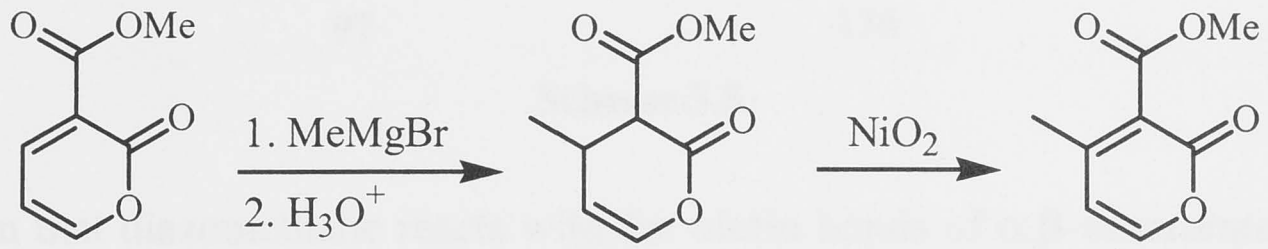
Scheme 3.1

Our initial approach to **136** is outlined in Scheme **3.2**. Diol **138** was selectively oxidised with ceric ammonium nitrate and sodium bromate.[62] After protection of the terminal hydroxyl as a silyl ether, the product **139** underwent a Knoevenagel-type reaction with methyl cyanoacetate (**140**) to afford a 50/50 mixture of isomers **141** and **142**. Hydrolysis of **141** produced pyrone precursor **143**, but although it was probable that **143** could be converted to **136**, poor yields in the previous steps prompted us to search for alternative routes.



Scheme 3.2

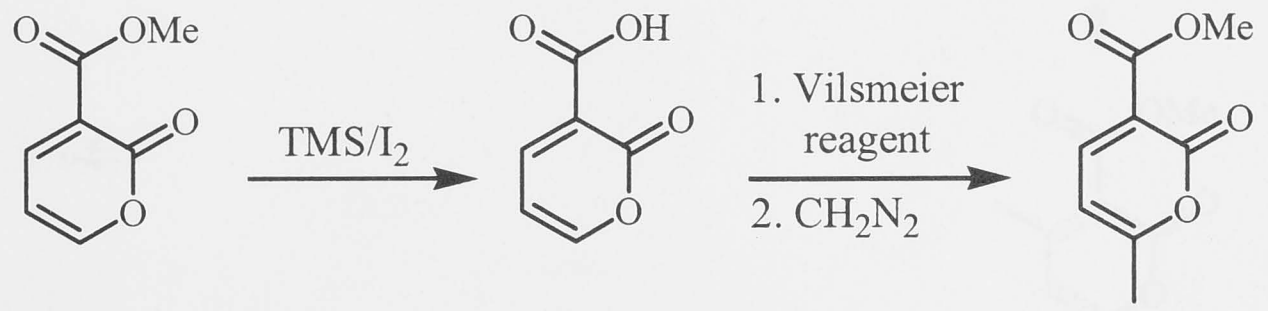
Examples of suitably substituted pyrones in the literature were remarkably scarce. However, in a paper on the synthesis of ionophore antibiotics, Ireland made reference to the introduction of an ethyl group into the 4-position using a suitable Grignard reagent, followed by oxidation with nickel peroxide to furnish the substituted pyrone.[63] After treatment of **97** with ethyl magnesium bromide and acidic work-up, dihydropyrone **144** was obtained in 54% yield (Scheme **3.3**). Rearomatisation to pyrone **136** with nickel peroxide proceeded in 82% yield.



97 **144** **136**

Scheme 3.3

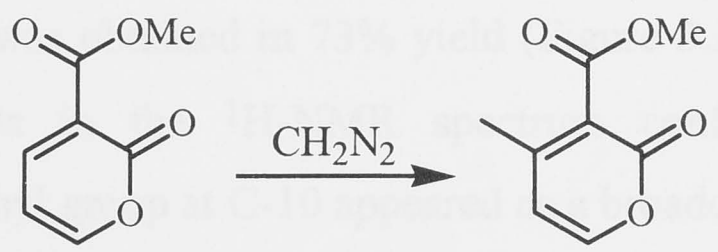
During the course of some earlier work aimed at homologating the carboxy ester group in **97** *via* the derived acyl chloride, we noted the formation of a compound to which we had assigned structure **146** (Scheme **3.4**). It appeared as though adventitious water had hydrolysed the intermediate acid chloride, and methylation of the acid with diazomethane was responsible for the presence of a large singlet at 3.91 ppm in the ^{1}H-NMR spectrum. Of greater interest was the disappearance of the most downfield proton signal at 8.25 ppm and the presence of a large singlet at 2.26 ppm. The two remaining olefinic signals were shifted upfield and simplified from doublets of doublets to doublets, both with a coupling of 5.4 Hz. We had assumed that the loss of the signal at 8.25 ppm represented substitution at C-6 (*i.e.* the carbon directly attached to oxygen). We were agreeably surprised, therefore, to discover that the both the ^{1}H-NMR and ^{13}C-NMR spectra were an exact match for **136**.



97 **145** **146**

Scheme 3.4

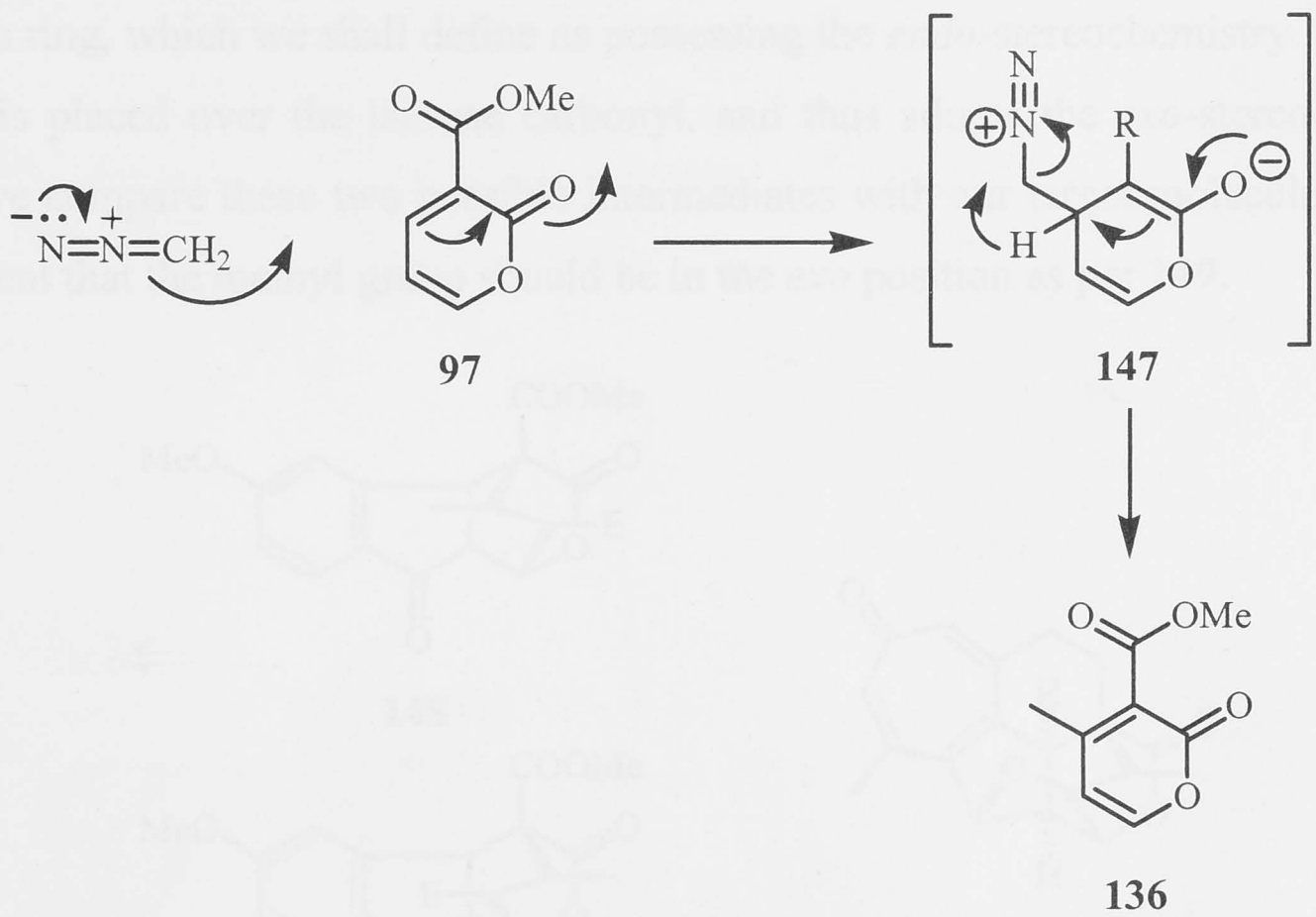
Indeed, when ethereal diazomethane was added to a solution of **97**, an 82% yield of **136** was obtained and unlike the Ireland procedure, which was noted as being capricious, the reaction could be carried out easily on a 10 g scale (Scheme **3.5**).



97 **136**

Scheme 3.5

It is known that diazomethane reacts with the olefin bonds of α,β-unsaturated esters or ketones producing a pyrazoline which loses nitrogen on heating, usually to form a mixture of a substituted cyclopropane and the β-methyl analogue of the original olefin.[64,65] However, in the present case the mechanism for the reaction most likely involves a Whitmore hydride shift, as seen in the reaction of diazomethane with α-cyanocrotonic acid[66] and similarly with methyl coumalate.[67] Nucleophilic attack by diazomethane at the electron deficient site C4 of the pyrone could be expected to give the unstable intermediate **147**. A hydride shift as outlined in Scheme **3.6** results in evolution of nitrogen and formation of the desired product **136**.

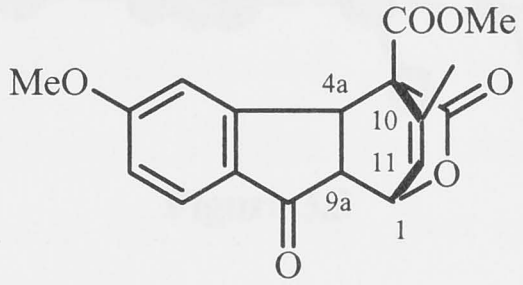


97 **147** **136**

Scheme 3.6

SECTION 3.2 Manipulation of the Bridge Stereochemistry

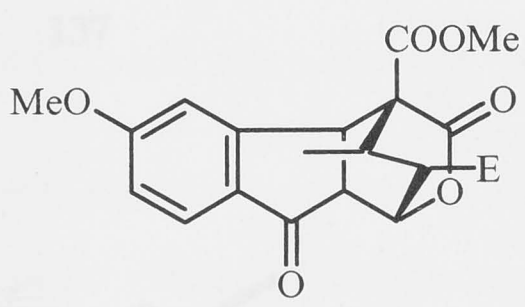
When the newly prepared pyrone **136** and indenone **93** were subjected to 19 Kbar for 20 hours, cycloadduct **137** was obtained in 73% yield (Figure **3.1**). A coupling of 4.9 Hz between H-1 and H-9a in the ^{1}H-NMR spectrum confirmed the compound's regiochemistry. The methyl group at C-10 appeared as a broadened singlet at 1.55 ppm., with the vinyl proton as a doublet at 5.97 ppm. The upfield shift of 0.39 ppm relative to cycloadduct **98** was presumably a consequence of the electron donating effect of the adjacent methyl.



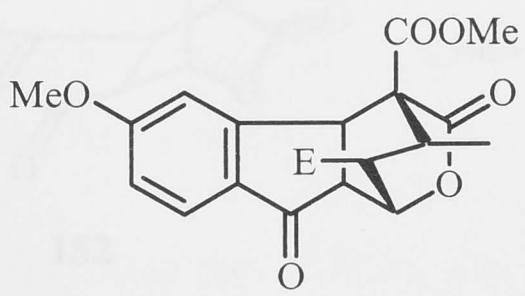
137

Figure 3.1

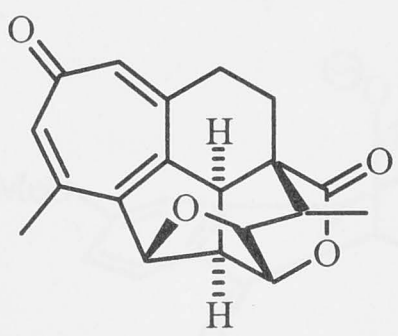
Elaboration of **137** poses an interesting problem. Attack of electrophilic reagent H-E can theoretically occur on either face of the double bond, leading to the formation of two possible products (Figure **3.2**). With **148**, the methyl group is positioned over the aromatic ring, which we shall define as possessing the *endo*-stereochemistry. In **149** the methyl is placed over the lactone carbonyl, and thus adopts the *exo*-stereochemistry. When we compare these two possible intermediates with our target molecule **1**, then it is apparent that the methyl group should be in the *exo* position as per **149**.



148



149



1

Figure 3.2

However, when we examine a side-on view of cycloadduct **137** (Figure **3.3**) we see that one face is much less hindered. Approach of the electrophile along the indicated vector is clearly more favourable and will result in an *endo*-methyl. We therefore required a synthetic plan that would enable us to control the methyl configuration.

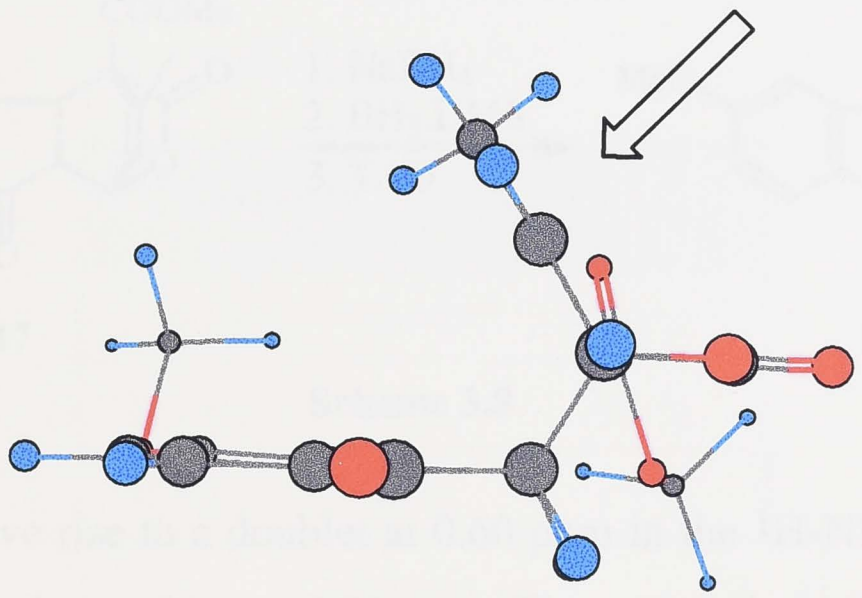
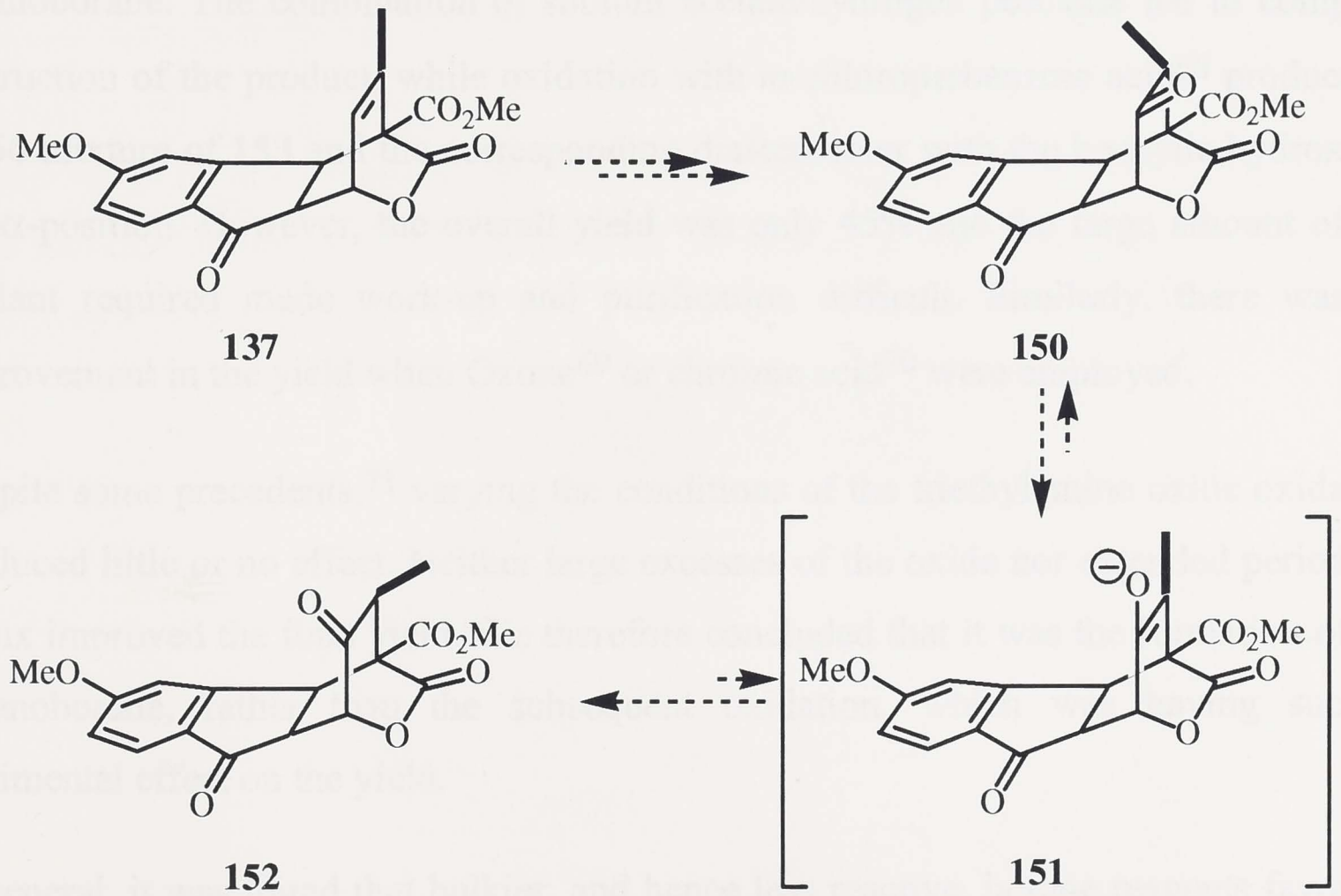


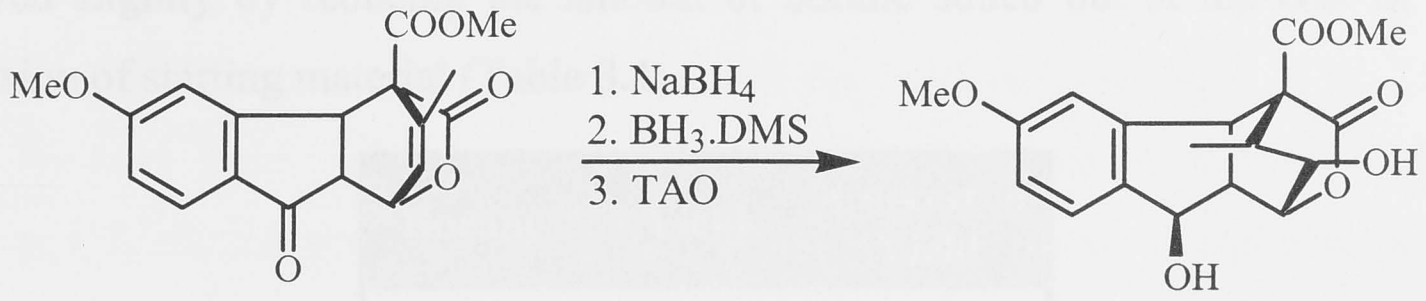
Figure 3.3

Hydroboration of the double bond followed by oxidation was expected to provide us with intermediate **150** with the methyl in the *endo* position (Scheme **3.7**). Treatment of **150** with a suitable base was expected to generate enolate **151** and although a proton may approach from either face of the olefinic bond, a gradual accumulation of the thermodynamic *exo* product **152** was predicted if the system was kept in equilibrium.



Scheme 3.7

Ketone **137** was reduced to the benzylic alcohol in 85% yield, then borane-dimethyl sulfide addition followed by oxidation with triethylamine oxide was ultimately found to provide the best conditions for the hydroboration step, although **153** was obtained in only 49% yield (Scheme **3.8**).



137 **153**

Scheme 3.8

The methyl group gave rise to a doublet at 0.60 ppm in the ^{1}H-NMR spectrum, with a coupling of 7.2 Hz to the methine at 2.31 ppm. The unusually high field chemical shift of the methyl can be attributed to the shielding effect of the aromatic ring. H-11 was observed as a doublet at 4.08 ppm with a coupling to H-10 of 5.5 Hz. C10 and C11 appeared at 83.19 and 41.98 ppm in the ^{13}C-NMR spectra respectively. Formation of the diol was also confirmed by the presence of a molecular ion at *m/z* 348 in the mass spectrum.

In our efforts to improve the yield, we initially investigated the oxidation of the organoborane. The combination of sodium acetate/hydrogen peroxide led to complete destruction of the product, while oxidation with *m*-chloroperbenzoic acid[68] produced a 50/50 mixture of **153** and the corresponding diastereomer with the benzylic hydroxy in the α-position. However, the overall yield was only 45% and the large amount of the oxidant required made work-up and purification difficult. Similarly, there was no improvement in the yield when Oxone[69] or chromic acid[70] were employed.

Despite some precedents,[71] varying the conditions of the triethylamine oxide oxidation produced little or no effect. Neither large excesses of the oxide nor extended periods of reflux improved the final yield. We therefore concluded that it was the formation of the organoborane, rather than the subsequent oxidation, which was having such a detrimental effect on the yield.

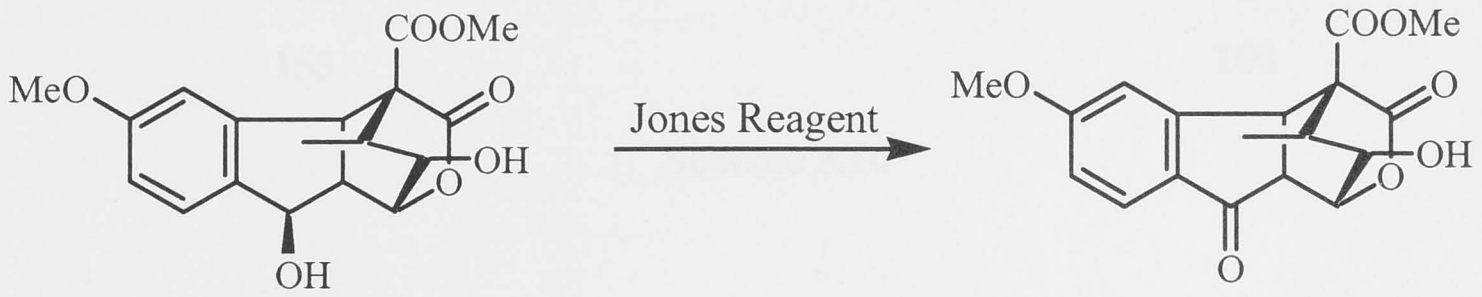
In general, it was found that bulkier, and hence less reactive, borane reagents favoured attack on the lactone carbonyl rather than on the double bond. Thus, when thexylborane was used, the olefinic proton was clearly visible in the ^{1}H-NMR spectrum of the

product. Similarly, reflux of **137** with 9-BBN resulted in CO_2 extrusion. Other borane reagents simply returned starting material (e.g. BH_2Cl-THF). In fact, only borane-dimethyl sulfide and borane-tetrahydrofuran furnished **153**. Neither changes in the solvent, temperature nor reaction time had any noticeable effect. Overall yields could be improved slightly by reducing the amount of borane added but at the cost of lower conversion of starting material (Table **3.1**).

Borane	Yield	Corrected Yield
1.0 eq	49 %	49 %
0.8 eq	46 %	54 %
0.6 eq	40 %	57 %

Table 3.1

Surprisingly, when **153** was treated with Jones' reagent, **154** was obtained rather than the desired diketone (Scheme **3.9**).



153 **154**

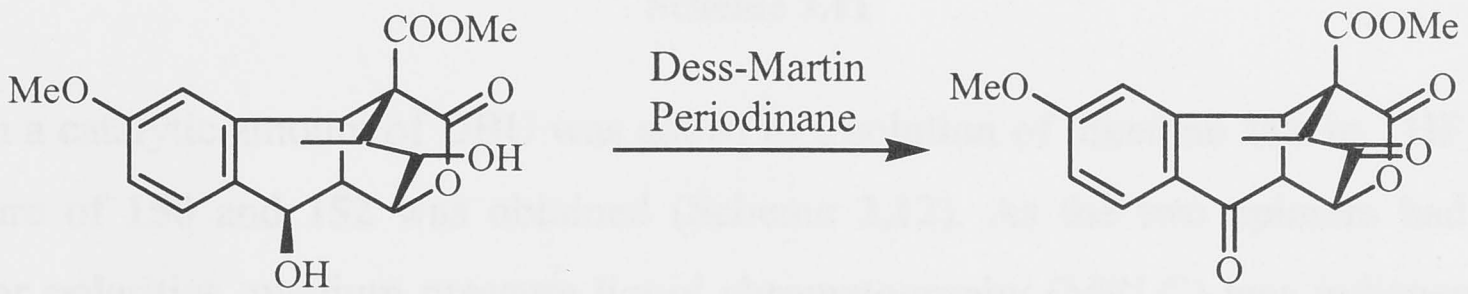
Scheme 3.9

When a range of other oxidants was tested, **154** was primarily obtained (Table **3.2**). A small amount of the desired product was formed as a minor product when Swern conditions[72] were employed.

Reagent	Result
Jones	**154**
PCC	**154**
PDC	**154**
TPAP	**154**
SO_3.Pyr/DMSO	**153**
Swern	Mixture

Table 3.2

Diketone **150** was eventually prepared in 48% yield with the Dess-Martin periodinane (Scheme **3.10**).[73] The diketone was characterised by the two peaks at 203.20 and 196.45 ppm (C11 and C9 respectively) in the ^{13}C-NMR spectrum and a downfield shift of 0.86 ppm for H-10. Efforts to improve the yield were unsuccessful, despite the presence of only one product, **150**, in the crude proton spectrum. However, complexing of the periodinane with *tert.*-butyl alcohol[74] reduced the reaction time from 16 to 2 hours. While we have been unable to definitively establish the basis for the low yield, this result and literature precedent suggest that the diol remains complexed with the periodinane and the resulting alkoxyperiodinane is not hydrolysed under the standard $NaHCO_3/Na_2S_2O_3$ conditions.

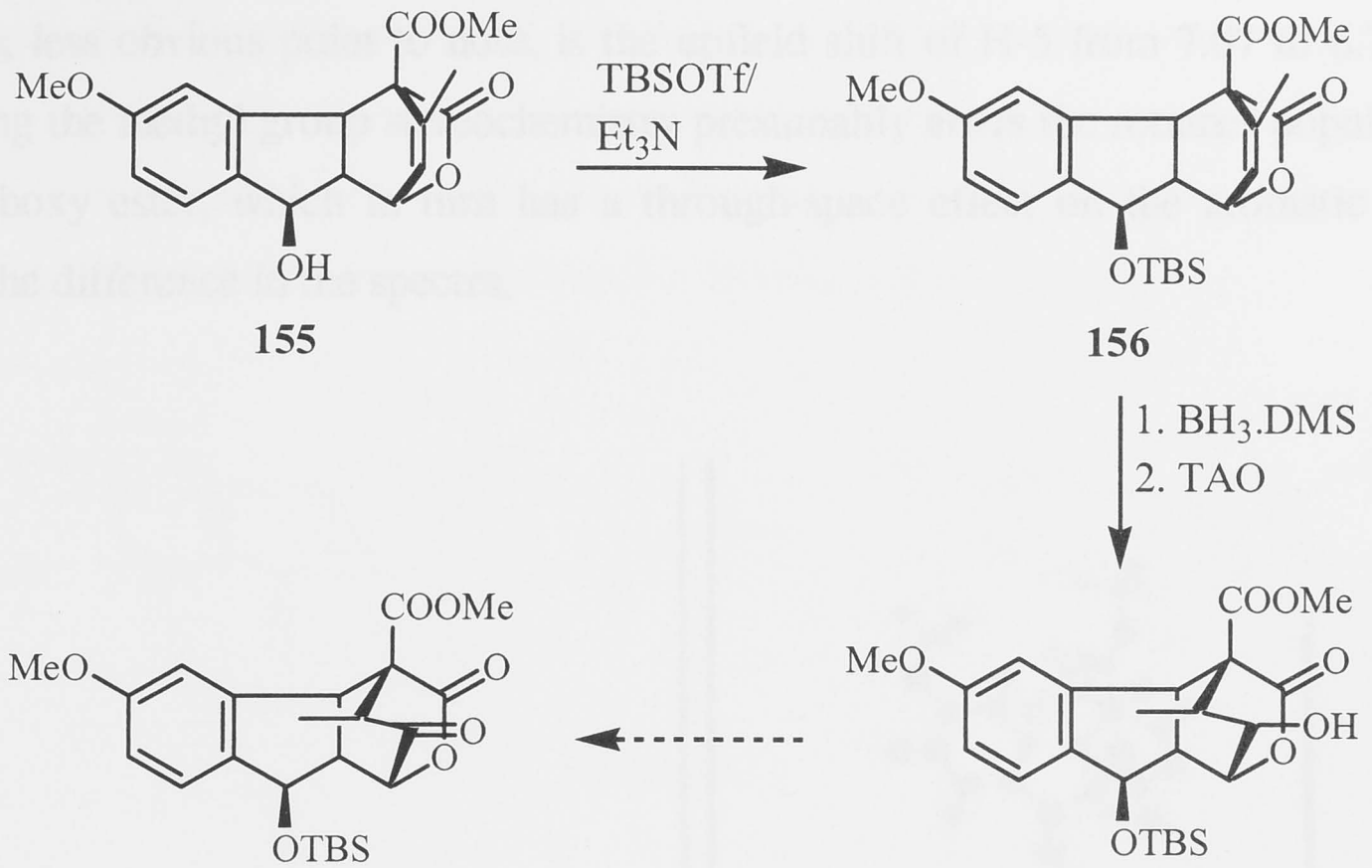


153 **150**

Scheme 3.10

Given the difficulties with the hydroboration and oxidation steps, we decided to protect **155** as a silyl ether (Scheme **3.11**). This was expected to significantly decrease the compound's polarity and thus facilitate recovery during workup. It would also mean that less borane and periodinane would be required, and this would hopefully have a beneficial effect on the overall yield of the diketone.

Addition of *tert.*-butyldimethylsilyl triflate to a mixture of the benzylic alcohol and triethylamine afforded **156** in 73% yield. **157** was prepared as before using borane-dimethyl sulfide and triethylamine oxide. Disappointingly, the yield remained low at 51% and subsequent attempts to convert **157** to **158** were unsuccessful. We therefore decided to persevere with our earlier approach.



155 **156** **158** **157**

Scheme 3.11

When a catalytic amount of DBU was added to a solution of diketone **150** in THF a 1:4 mixture of **150** and **152** was obtained (Scheme **3.12**). As the two epimers had very similar polarities, medium pressure liquid chromatography (MPLC) was indispensable when performing separations.

150 **152**

Scheme 3.12

The transformation of **150** to **152** was manifestly apparent from the ^{1}H-NMR spectrum. The bridge methyl which had appeared as a doublet at 0.49 ppm (Figure **3.4**) for **150**, now had a chemical shift of 1.35 ppm in **152** (Figure **3.5**). This large downfield shift can be ascribed to the removal of the methyl group from the shielding effect of the aromatic ring.

Conversely, the corresponding methine proton, which is rendered as a quartet, was shifted upfield from 3.17 ppm to 2.34 ppm. This change is attributable to the methine proton adopting the *endo*-stereochemistry and moving into close proximity to the π electrons of the benzene ring.

A third, less obvious point to note, is the upfield shift of H-5 from 7.07 to 6.75 ppm. Inverting the methyl group stereochemistry presumably alters the rotamer population of the carboxy ester, which in turn has a through-space effect on the aromatic proton; hence the difference in the spectra.

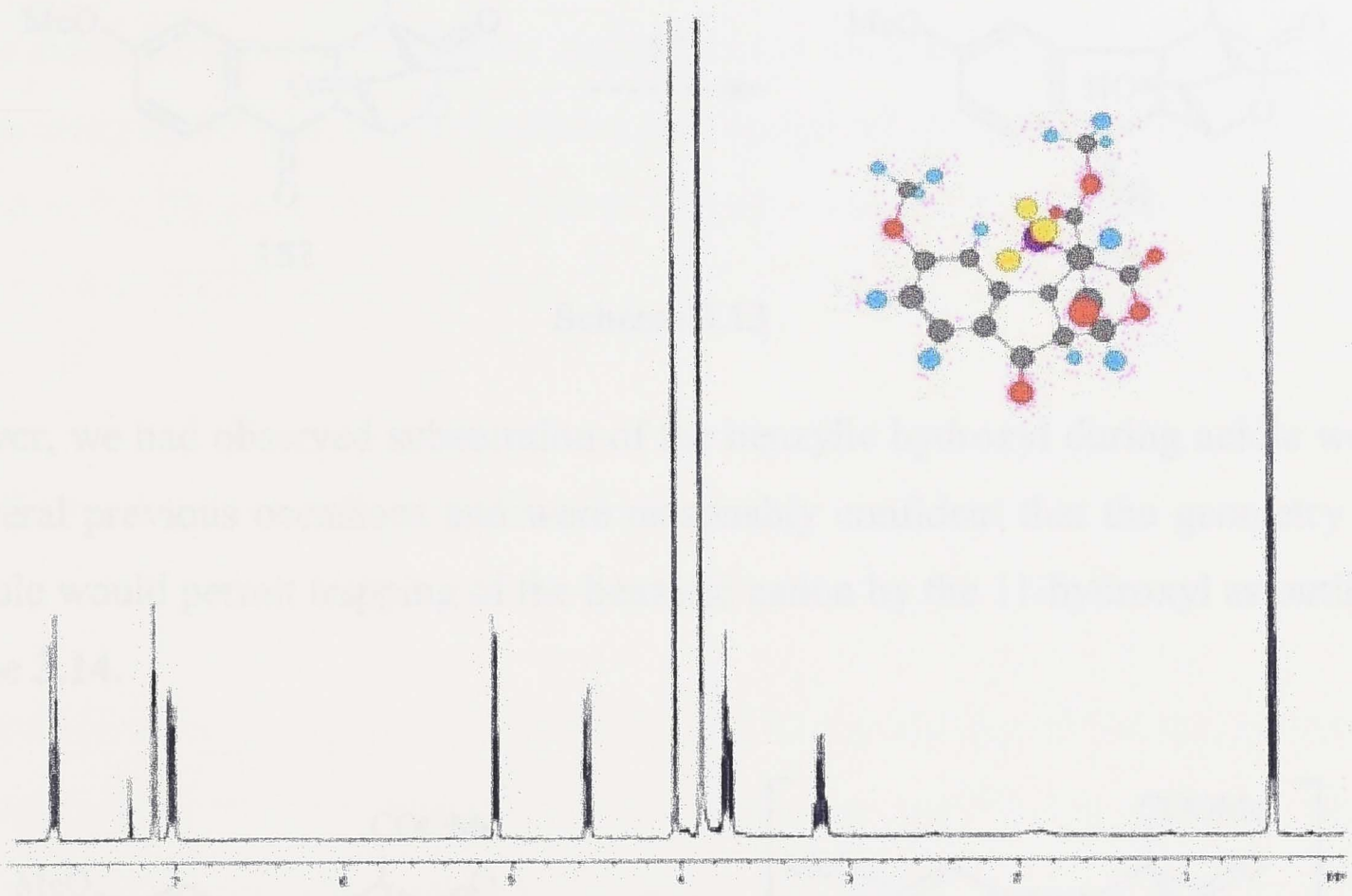


Figure 3.4

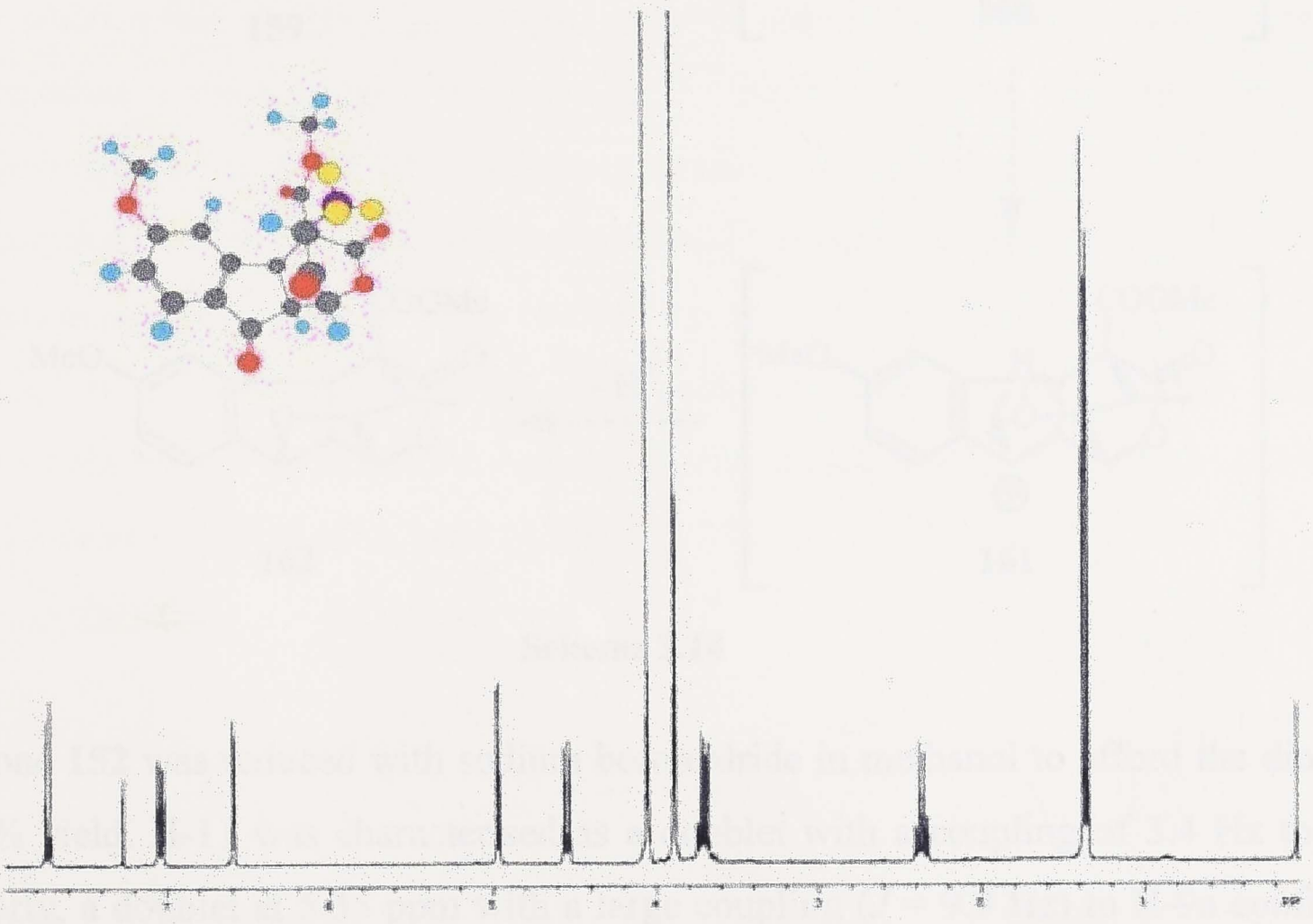
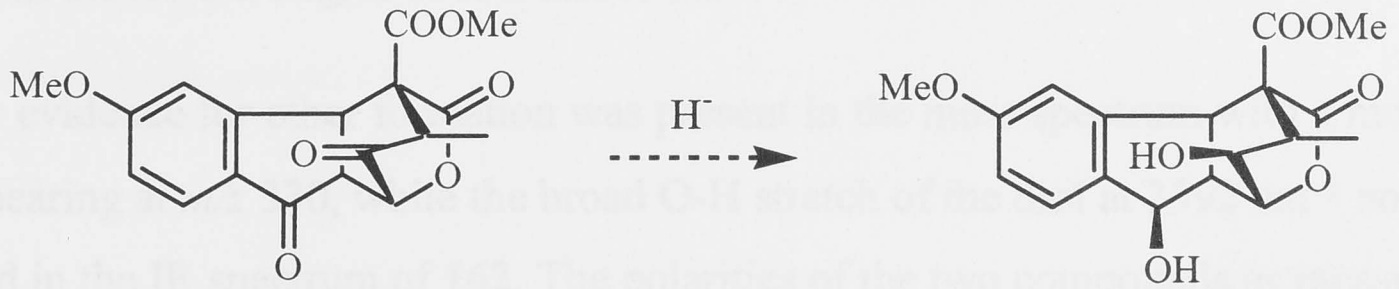


Figure 3.5

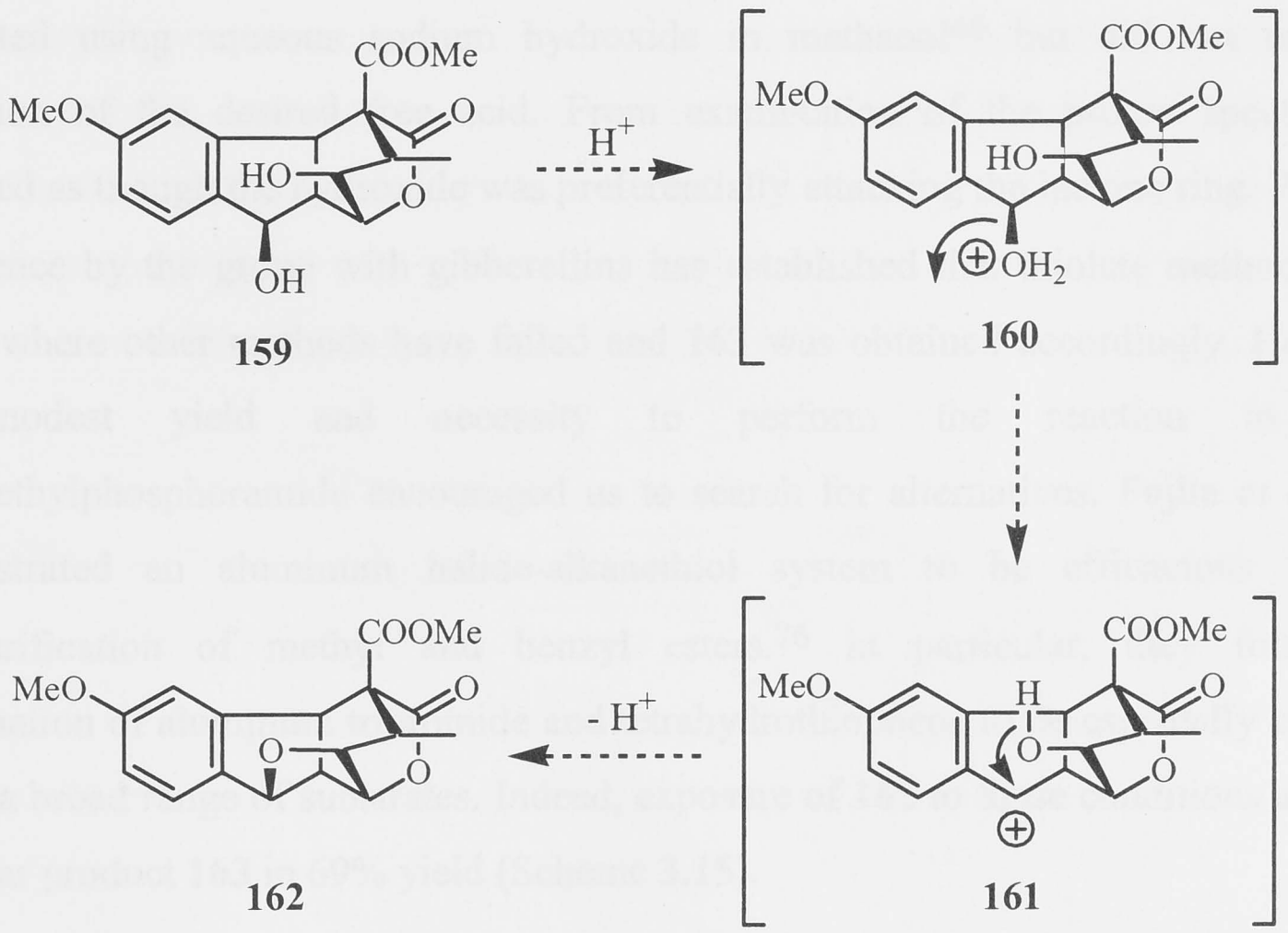
It was expected from the shape of **152** that it would be reduced to the *syn* diol **159** (Scheme **3.13**). Clearly, formation of the desired ether from this isomer did not appear to be an attractive prospect as the stereochemistry of the hydroxyls precluded ether formation by S_N2 displacement of a suitable leaving group.



152 **159**

Scheme 3.13

However, we had observed substitution of the benzylic hydroxyl during acidic work-up on several previous occasions and were reasonably confident that the geometry of the molecule would permit trapping of the benzylic cation by the 11-hydroxyl as outlined in Scheme **3.14**.



159 **160**

162 **161**

Scheme 3.14

Diketone **152** was reduced with sodium borohydride in methanol to afford the diol **159** in 66% yield. H-11 was characterised as a doublet with a coupling of 3.4 Hz to H-1. Similarly, a doublet at 5.35 ppm with a large coupling (J = 9.9 Hz) to H-9a confirmed that the benzylic ketone had been reduced. C11 and C9 were represented by peaks at 78.64 and 74.34 ppm respectively in the ^{13}C-NMR spectra.

159 was converted to **162** and the tetrahydrofuran moiety established on treatment with *p*-toluenesulfonic acid. No major changes were immediately apparent in the ^{1}H-NMR spectrum of **162** relative to **159**. However, a smaller coupling of 5.0 Hz between H-9 and H-9a as compared to 9.9 Hz in **159** is indicative of ether formation which forces a change in the torsion angles of H-9 and H-9a.

Further evidence for ether formation was present in the mass spectrum with a molecular ion appearing at *m/z* 330, while the broad O-H stretch of the diol at 3392 cm^{-1} no longer featured in the IR spectrum of **162**. The polarities of the two compounds as measured by TLC were also significantly different.

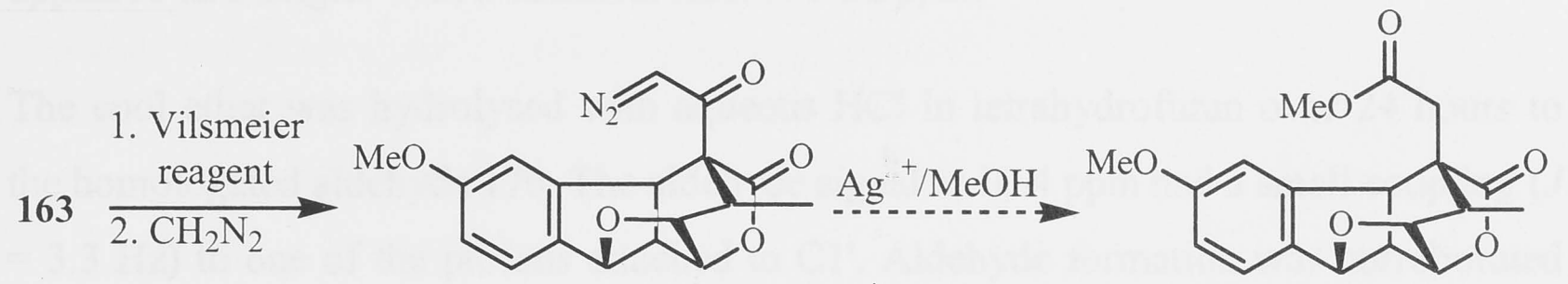
SECTION 3.3 Side Chain Homologation

As a prelude to homologating the carboxyl in **162**, hydrolysis of the methyl ester was attempted using aqueous sodium hydroxide in methanol[46] but did not result in formation of the desired free acid. From examination of the proton spectrum, it appeared as though the hydroxide was preferentially attacking the lactone ring. Previous experience by the group with gibberellins has established that thiolate methods[75] are useful where other methods have failed and **163** was obtained accordingly. However, the modest yield and necessity to perform the reaction in toxic hexamethylphosphoramide encouraged us to search for alternatives. Fujita *et al* have demonstrated an aluminum halide-alkanethiol system to be efficacious for the desesterification of methyl and benzyl esters.[76] In particular, they found the combination of aluminum tribromide and tetrahydrothiophene to be especially effective across a broad range of substrates. Indeed, exposure of **162** to these conditions afforded the polar product **163** in 69% yield (Scheme **3.15**).

162 **163**

Scheme 3.15

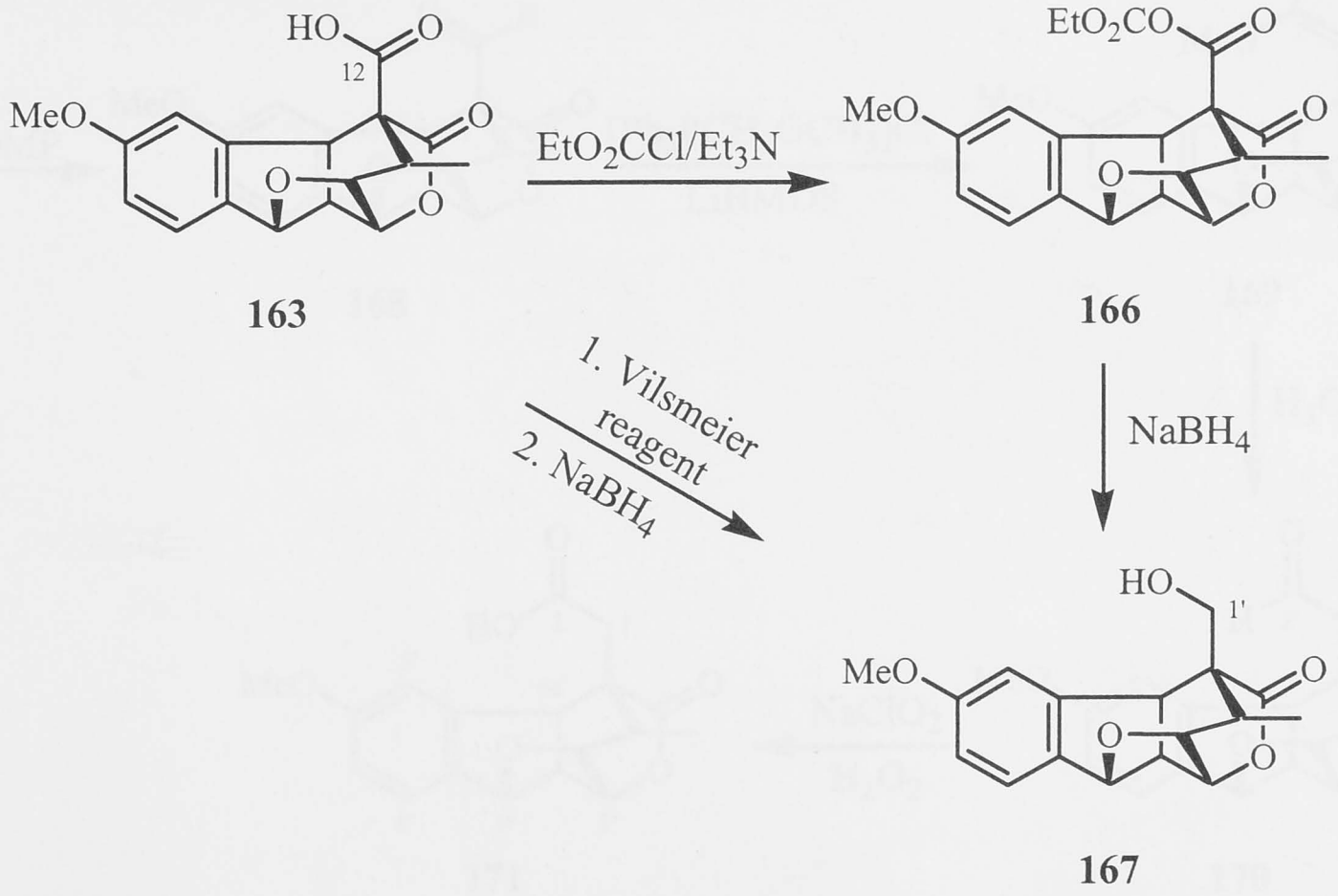
163 was converted to the acid chloride using the Vilsmeier reagent, which was then added to an excess of ethereal diazomethane to afford diazoketone **164** in 53% overall yield (Scheme **3.16**). The proton α to the diazo group was rendered as a characteristically broad singlet at 6.02 ppm in the ^{1}H-NMR spectrum while the presence of a strong sharp band at 2106 cm^{-1} in the IR spectrum clearly indicated formation of diazocarbonyl compound **164**.



164 **165**

Scheme 3.16

Regrettably, attempts to transform **164** to **165** *via* an Arndt-Eistert homologation were unsuccessful despite recourse to a number of silver(I) based catalysts. However, we were hopeful that Wittig type chemistry might be more productive and undertook to reduce carboxylic acid **163** to the corresponding alcohol. Reduction of the mixed anhydride **166** resulted in a 1:3 ratio of **167** to starting material (Scheme **3.17**). However, conversion of **163** to the acid chloride followed by borohydride reduction proved to be much more effective, affording a 76% yield of **167**.

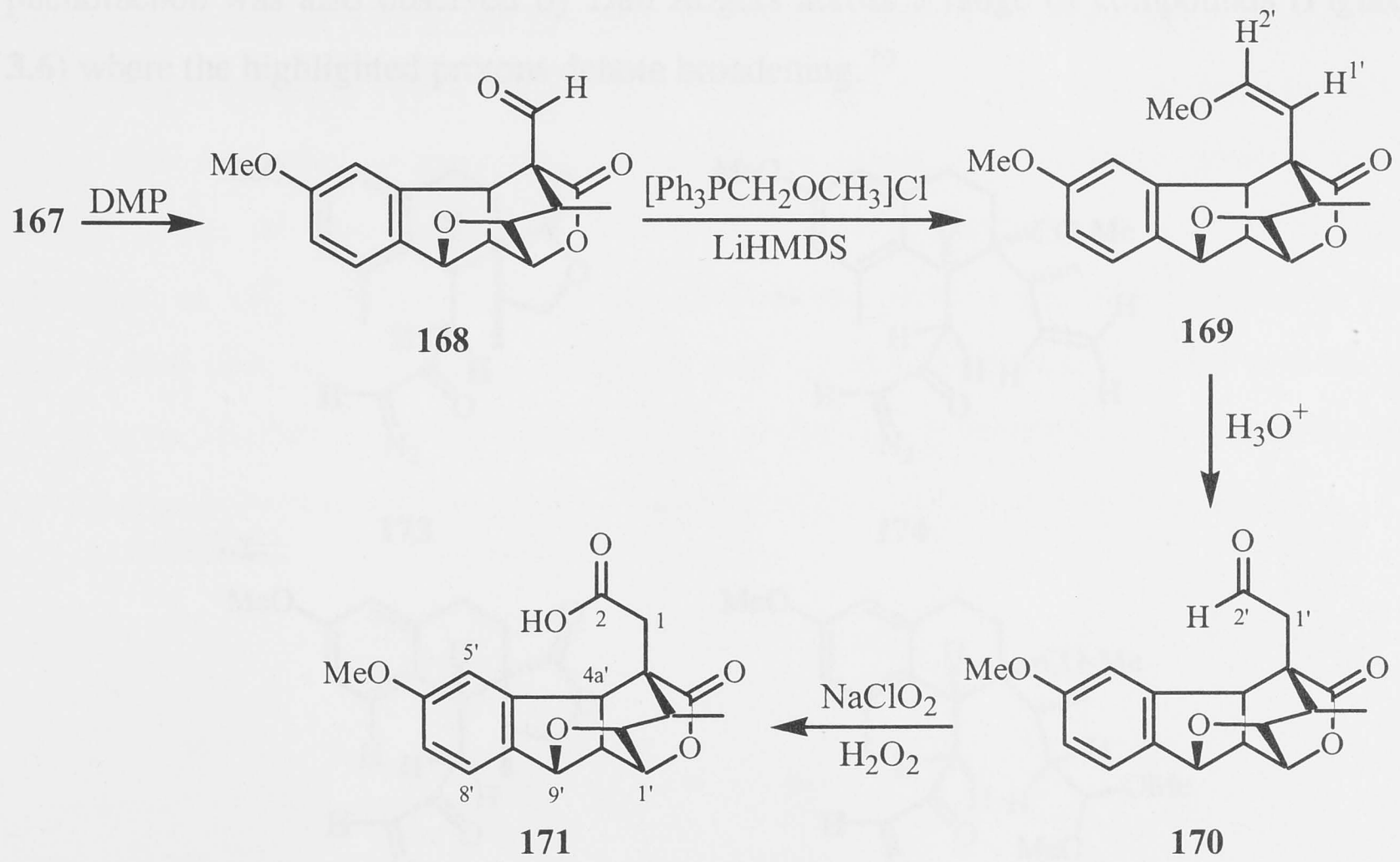


Scheme 3.17

Following oxidation of carbinol **167** to the aldehyde in excellent yield with the Dess-Martin periodinane, **168** was added to an excess of the methoxymethylene ylide, preformed from the treatment of dry $[Ph_3P^+CH_2OMe]Cl^-$ with lithium hexamethyldisilazide,[77] as outlined in Scheme **3.18**. The resultant (Z)-methylenol ether **169** was obtained in 58% yield. H-1' and H-2' were characterised by doublets at 4.35 and 6.16 ppm respectively, with a mutual coupling of 7.0 Hz. The methoxyl singlet appeared as a singlet with a chemical shift of 3.52 ppm.

The enol ether was hydrolysed with aqueous HCl in tetrahydrofuran over 24 hours to the homologated aldehyde **170**. The aldehyde signal at 10.4 ppm had a small coupling (J = 3.3 Hz) to one of the protons attached to C1'. Aldehyde formation was corroborated by the appearance of a quaternary carbon at 202.20 ppm in the ^{13}C-NMR spectrum.

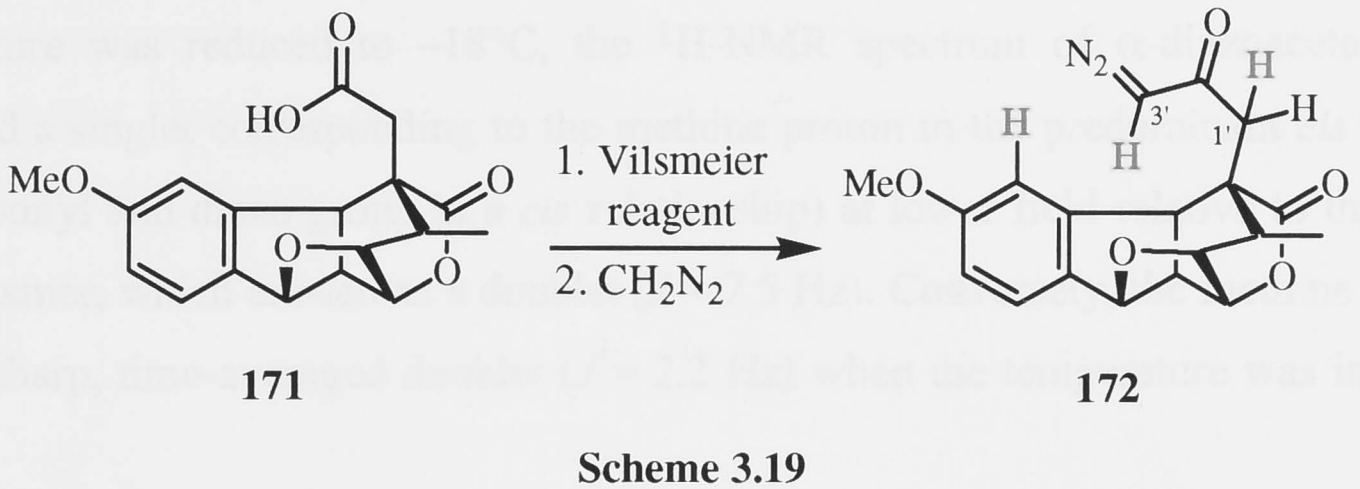
Attempted oxidation of **170** with Jones' reagent did not furnish any of the desired product. However, the combination of sodium chlorite and hydrogen peroxide with a phosphate buffer has previously been effective in the oxidation of aldehydes to carboxylic acids.[78] When **170** was treated accordingly with the above, the polar product **171** was obtained as a colourless oil. The loss of the aldehydic doublet in the ^{1}H-NMR spectrum, coupled with the appearance of C2 at 176.74 ppm, confirmed that the oxidation had occurred.



Scheme 3.18

SECTION 3.4 Attempted Arene Cyclopropanation

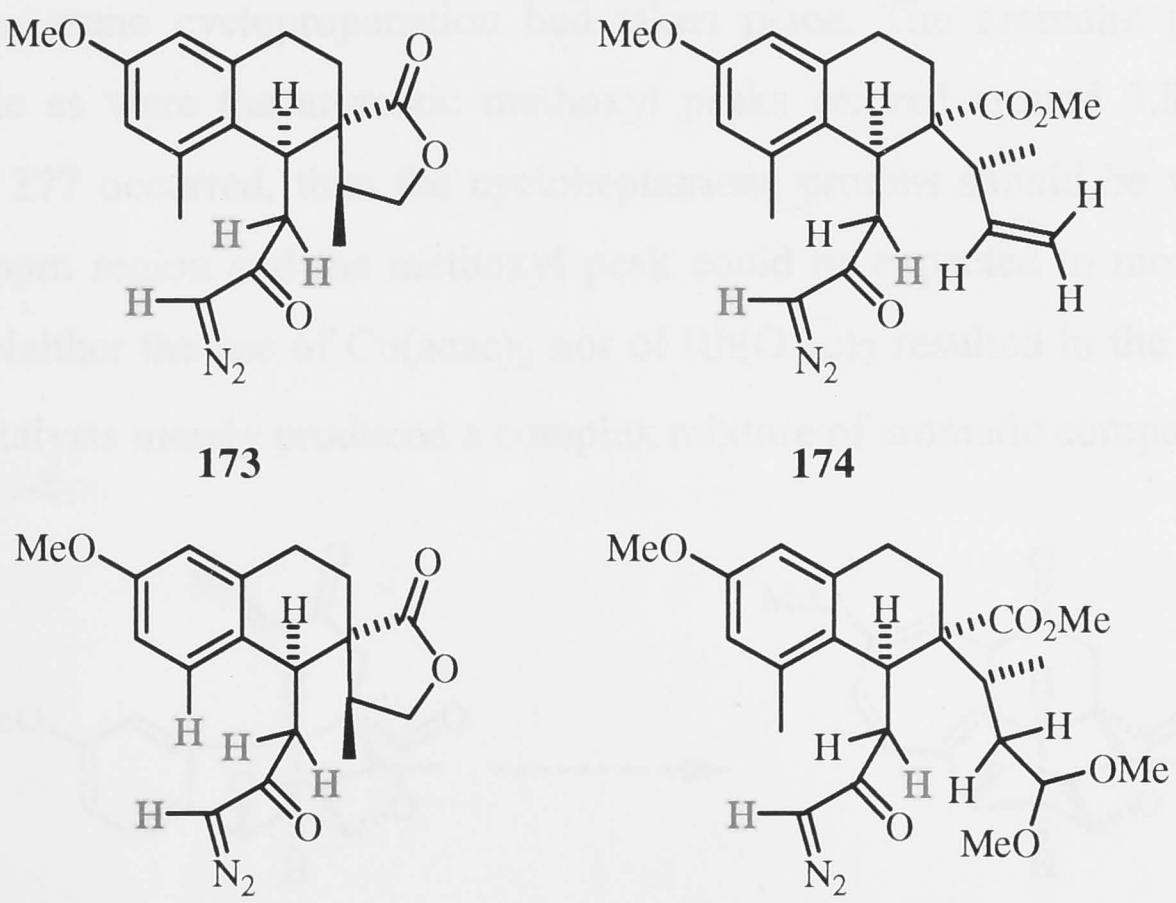
The acid chloride, generated by addition of the Vilsmeier reagent to a benzene solution of **171**, was converted to diazoketone **172** with ethereal diazomethane (Scheme **3.19**). A strong band at 2106 cm^{-1} in the IR spectrum was characteristic of the asymmetric diazo stretch. A molecular ion of *m/z* 354 was accompanied by a fragmentation pattern showing loss of nitrogen to produce a peak at *m/z* 328.



171 **172**

Scheme 3.19

The ^{1}H-NMR spectrum of **172** presents the C**H**N_2 proton as a broad singlet at 4.90 ppm. The two protons attached to C1' had chemical shifts of 2.83 and 2.25 ppm with a large geminal coupling of 15.5 Hz. Interestingly, although the more upfield proton was rendered as a sharp doublet, the second doublet was significantly broadened. This phenomenon was also observed by Dan Rogers across a range of compounds (Figure **3.6**) where the highlighted protons denote broadening.[79]



173 **174**

175 **176**

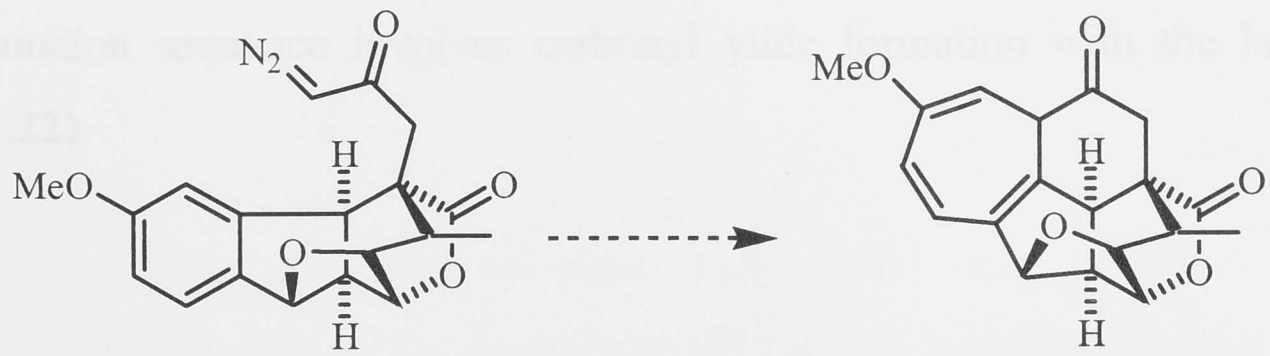
Figure 3.6

175 is especially noteworthy, for not only is there broadening of the methine and methylene protons, but also of the aromatic proton of closest proximity. A remarkably similar observation was noted with the broad doublet from H-5 in compound **172**.

In their studies of α-diazoacetaldehyde and α-diazoacetone, Kaplan and Melloy proposed that free rotation about the C-C bond might be hindered though the interaction of the π electrons of the α-carbon with the π system of the carbonyl group.[80] By performing variable temperature ^{1}H-NMR experiments, they managed to clearly show that the diazoketones exist as an equilibrium of *cis* and *trans* forms. When the temperature was reduced to –18°C, the ^{1}H-NMR spectrum of α-diazoacetaldehyde displayed a singlet corresponding to the methine proton in the predominant *cis* rotamer (*i.e.* carbonyl and diazo group in a *cis* relationship) at lower field relative to the minor *trans* rotamer, which existed as a doublet (J = 7.5 Hz). Conversely, the methine showed up as a sharp, time-averaged doublet (J = 2.2 Hz) when the temperature was increased to 71°C.

In the cases where only one of the methylene protons is broad while the other is a sharp doublet (e.g. **172**, **174** & **176**), the chemical shift of the unbroadened partner is apparently uninfluenced by the different rotamers. This indicates that it is geometrically situated such that it 'sees' both rotamers similarly.

Heating diazoketone **172** in the presence of bis(*N-t.*-butylsalicylaldiminato) copper(II) resulted in a complex mixture of products. Unfortunately, it was evident from the ^{1}H-NMR that no arene cyclopropanation had taken place. The aromatic protons were clearly visible as were the aromatic methoxyl peaks centred around 3.82 ppm. Had formation of **177** occurred, then the cycloheptatriene protons should be visible in the 5.30 – 6.00 ppm region and the methoxyl peak could be expected to move upfield to ~3.50 ppm. Neither the use of $Cu(acac)_2$ nor of $Rh(OAc)_2$ resulted in the formation of **177** - both catalysts merely produced a complex mixture of aromatic compounds.

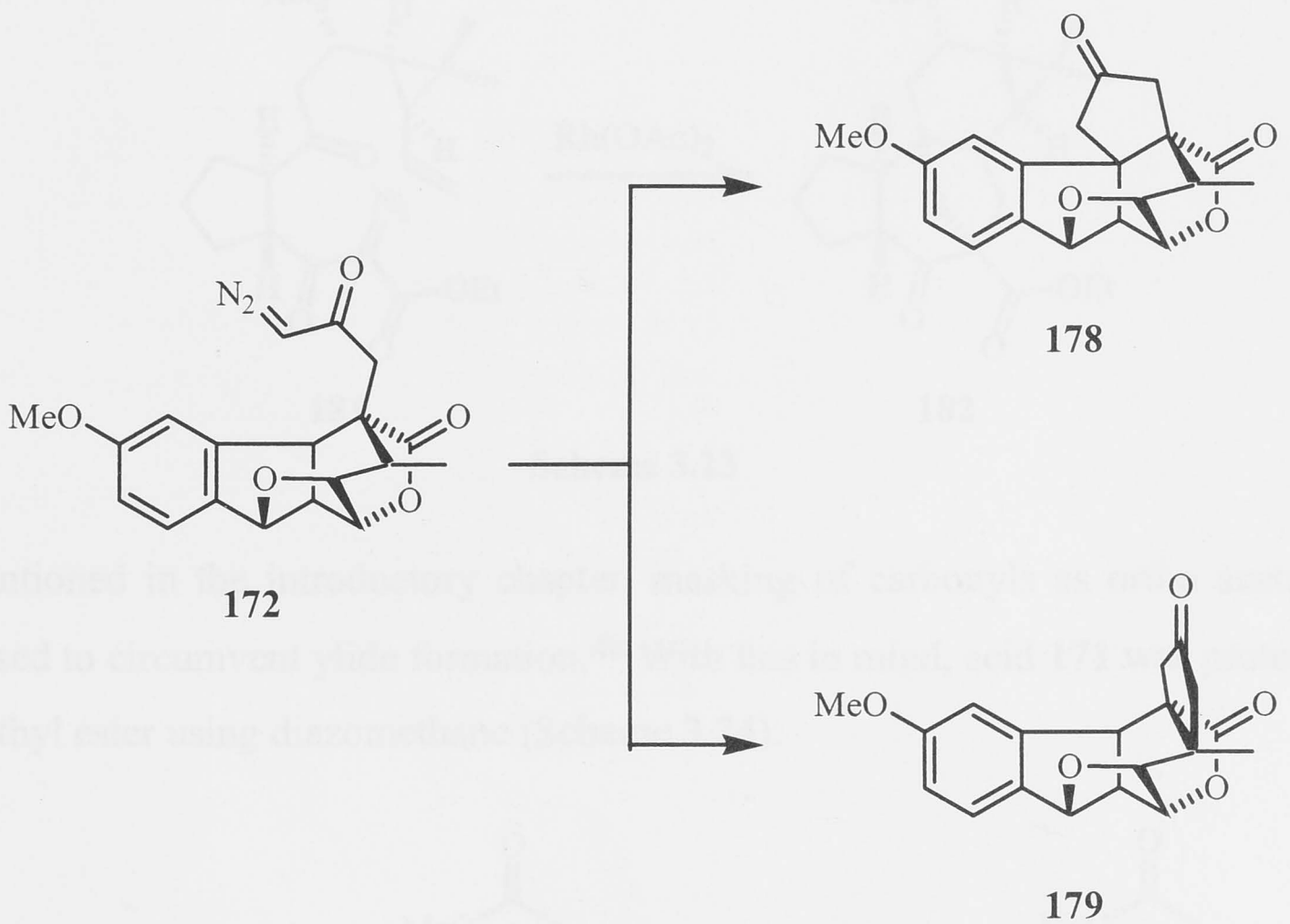


172 **177**

Scheme 3.20

There are a number of possibilities as to why the arene cyclopropanation did not proceed as expected. It is a well established fact that for intramolecular reactions, there is a preference for forming 5-membered rings over 6-membered rings due primarily to entropic factors.[81] Indeed, entropy considerations are often the most important and the formation of a 5-membered ring can override the preference for a more nucleophilic group if the latter results in the formation of a large (*i.e.* >6 membered) ring.[82]

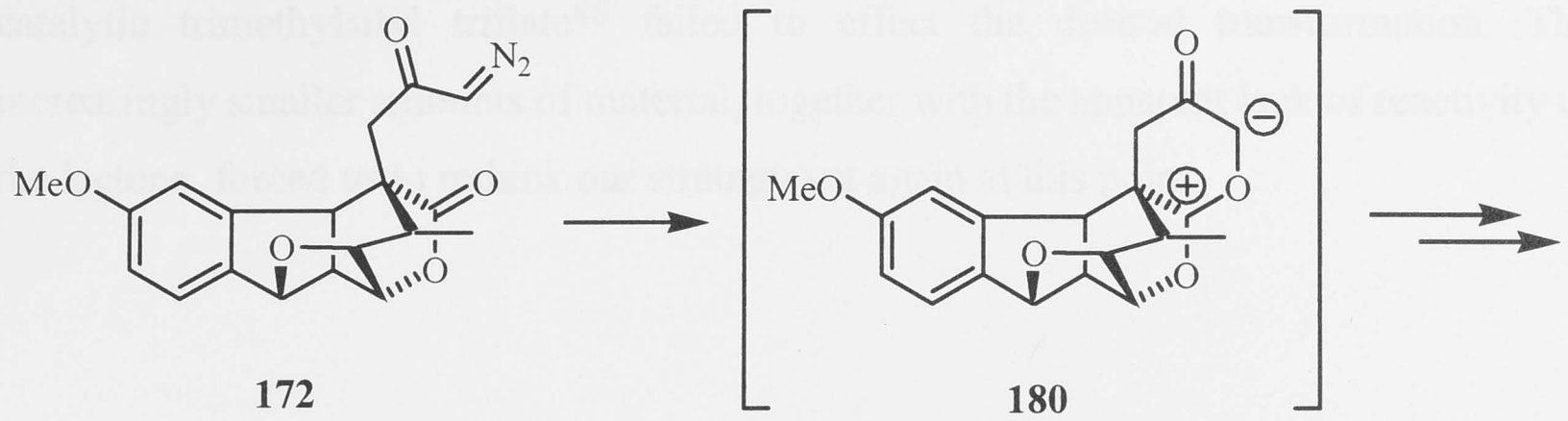
C-H insertion is another possibility. While benzylic C-H insertion as outlined in Scheme **3.21** to give **178** might appear be the more likely outcome, it is worth noting that the corresponding process was at no time observed during the model studies. In contrast, the alternative C-H insertion product **179** is now more favourable as a result of activation by the bridge methyl.



172 **178** **179**

Scheme 3.21

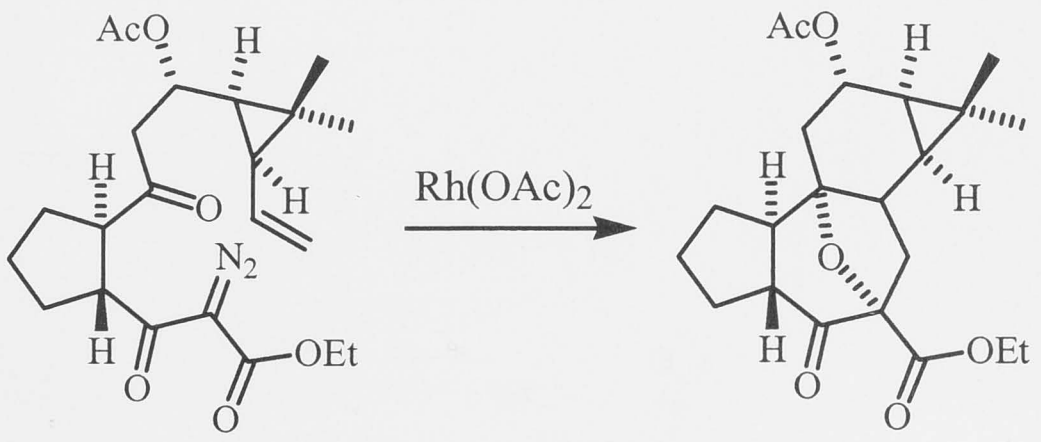
However, by far the most likely explanation for the failure of the arene cyclopropanation sequence involves carbonyl ylide formation with the lactone ring (Scheme **3.22**).



172 **180**

Scheme 3.22

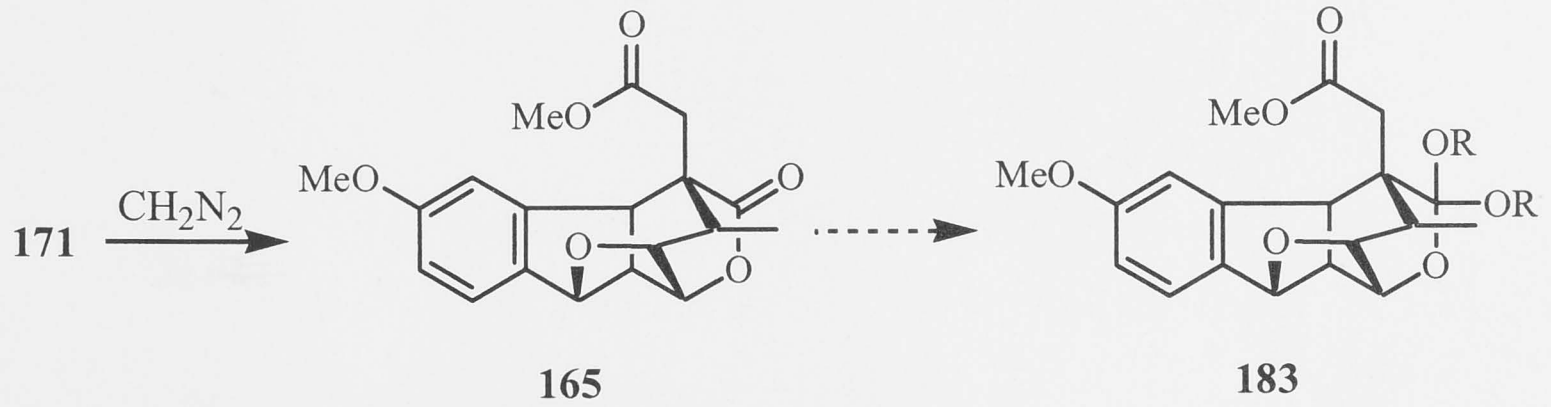
Extensive work in this area, especially that of Padwa,[83] has led to the practical application of this type of reaction to a number of synthetic challenges. For example, Dauben *et al.* utilised a rhodium(II) catalysed formation of a cyclic carbonyl ylide which was coupled to an intramolecular cycloaddition reaction to synthesise the C6-C9-oxido-bridged tigilane ring system **182** in an 86% yield.[84]



181 **182**

Scheme 3.23

As mentioned in the introductory chapter, masking of carbonyls as ortho acetals has been used to circumvent ylide formation.[48] With this in mind, acid **171** was protected as the methyl ester using diazomethane (Scheme **3.24**).



165 **183**

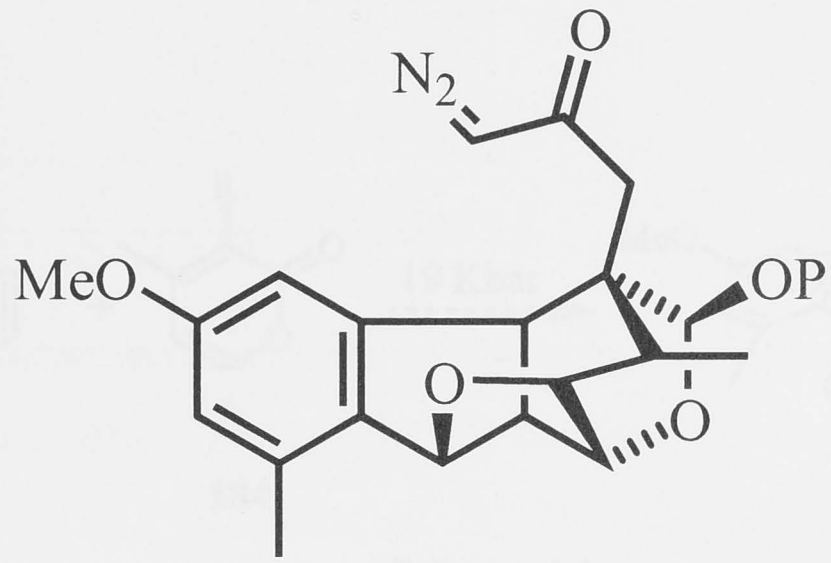
Scheme 3.24

Regrettably, we were unable to transform **165** to the ortho derivative **183**. Even powerful procedures such as the Meerwein salt method involving reactions with the triethyloxonium ion[85] and Noyori's method utilising methoxytrimethylsilane and

catalytic trimethylsilyl triflate[86] failed to effect the desired transformation. The increasingly smaller amounts of material, together with the apparent lack of reactivity of the lactone, forced us to rethink our strategy yet again at this point.

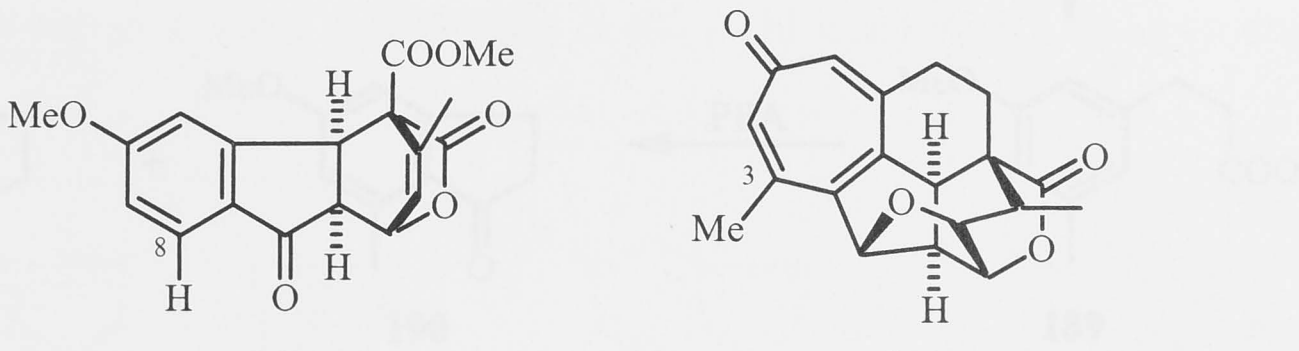
Chapter Four

Masking of the Lactone Carbonyl



SECTION 4.1 8-Methyl Indenone

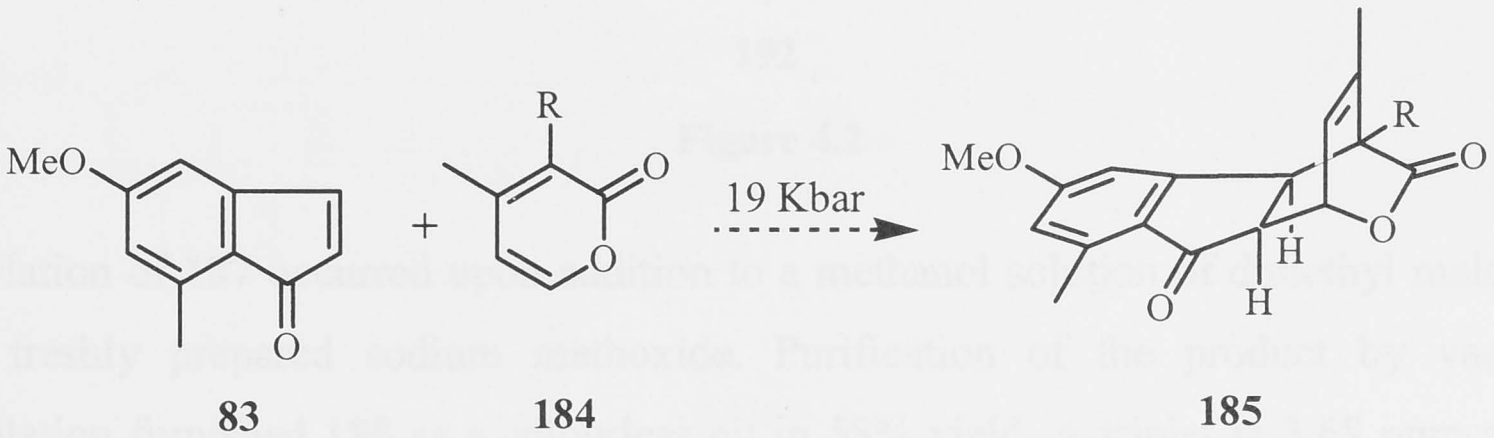
In our earlier work, we had prepared cycloadduct **137** which lacked the C8 aromatic methyl corresponding to the tropone methyl in harringtonolide (Figure **4.1**).



137 **1**

Figure 4.1

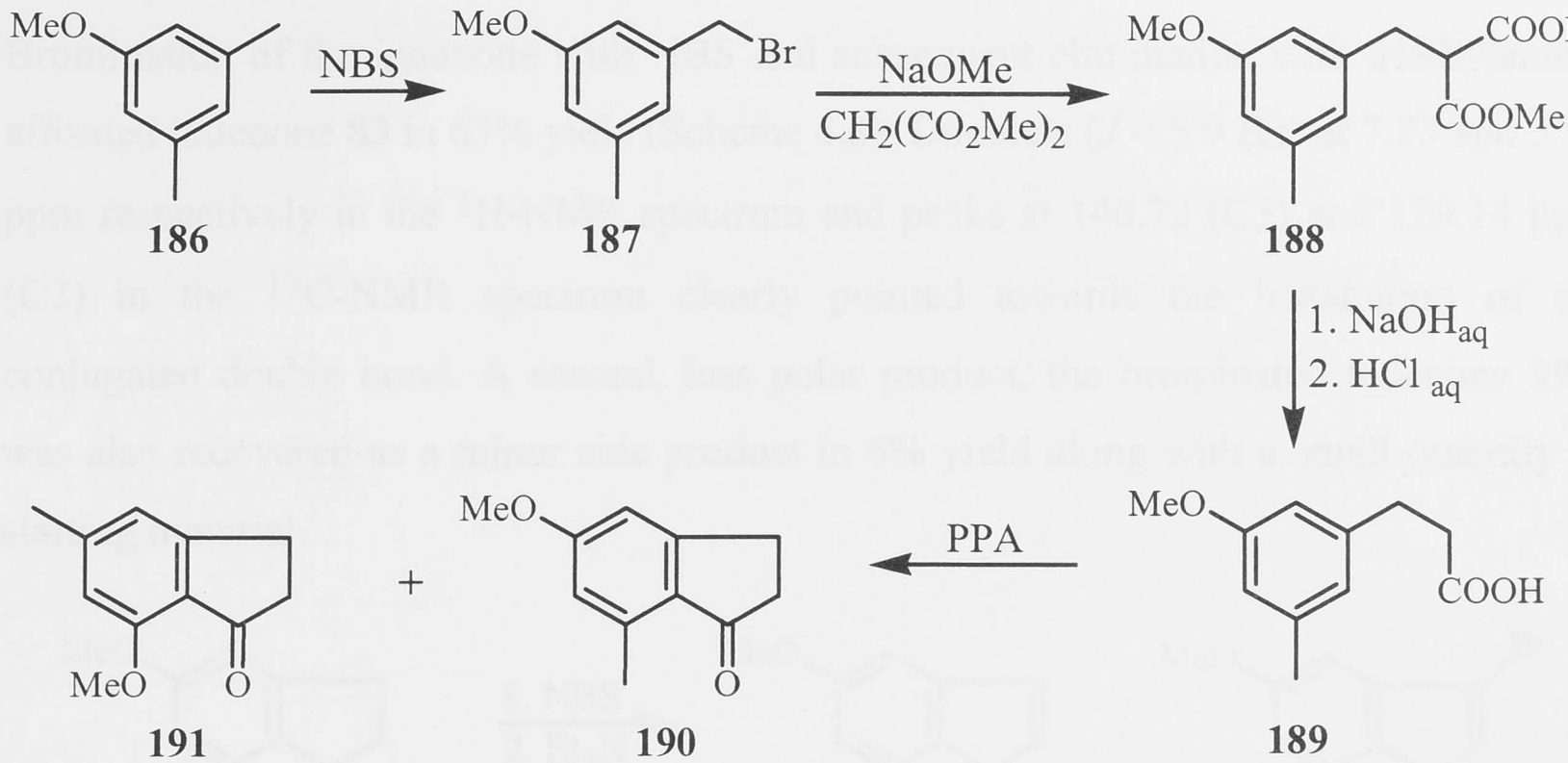
In order to rectify this situation, it was necessary to prepare 8-methyl indenone **83** (Scheme **4.1**). While the synthesis of the indanone precursor to **83** has previously been reported,[87] we encountered some difficulties in reproducing the reported yields. We therefore decided to develop a more direct approach to the indanone and from there proceed to **83**.



83 **184** **185**

Scheme 4.1

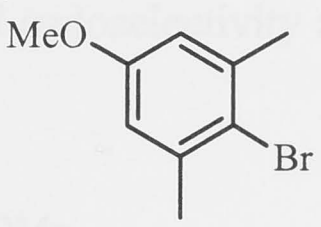
Anisole (**186**), obtained in excellent yield from dimethyl phenol, was treated with *N*-bromosuccinimide in CCl_4 under reflux and irradiated with tungsten lamps to produce the desired benzyl bromide **187** (Scheme **4.2**).[79]



186 **187** **188** **189** **191** **190**

Scheme 4.2

A ring-brominated by-product **192** (Figure **4.2**) was also recovered, although its formation could be minimised if the NBS reagent was recrystallised and thoroughly dried prior to use.



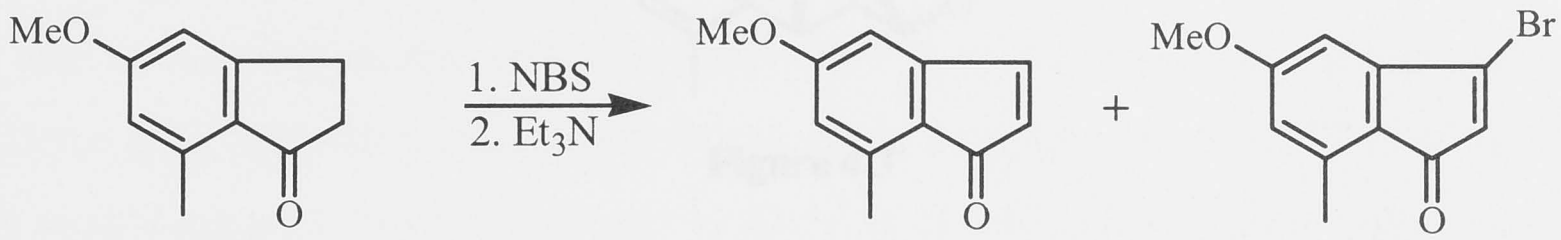
192

Figure 4.2

Alkylation of **187** occurred upon addition to a methanol solution of dimethyl malonate and freshly prepared sodium methoxide. Purification of the product by vacuum distillation furnished **188** as a colourless oil in 58% yield. A triplet at 3.68 ppm and a doublet at 3.15 ppm with a mutual coupling of 7.8 Hz confirmed that alkylation of the bromide had taken place.

Hydrolysis of the malonate in an aqueous solution of sodium hydroxide, followed by decarboxylation with concentrated hydrochloric acid, produced acid **189**, which was subsequently purified on a column of silica gel. Heating **189** in neat polyphosphoric acid for 30 minutes gave a 4.75:1 mixture of two isomers, **190** and **191**, on aqueous work-up. Separation by column chromatography resulted in a 57% yield of indanone **190** as colourless needles.

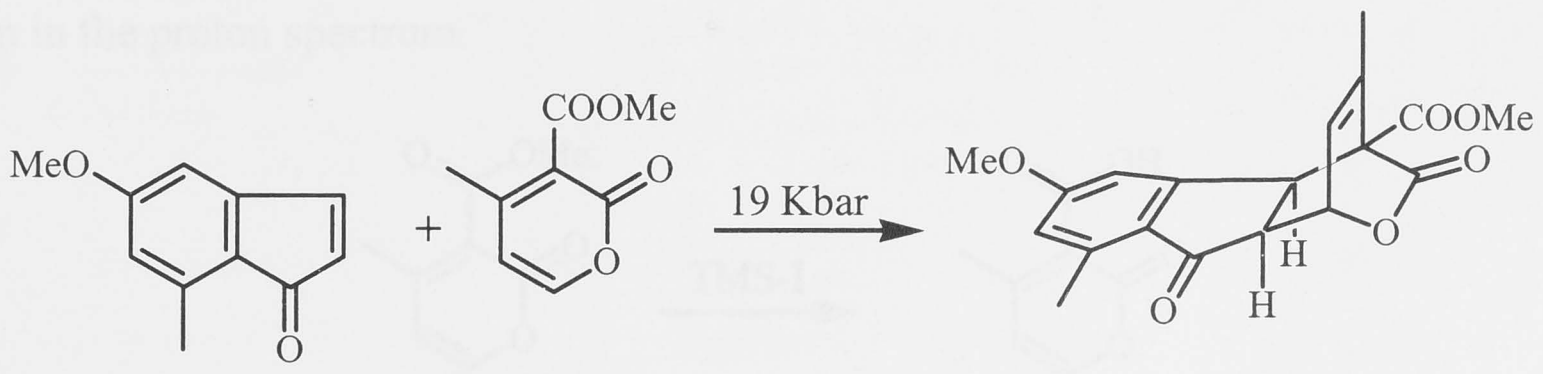
Bromination of the indanone with NBS and subsequent elimination with triethylamine afforded indenone **83** in 63% yield (Scheme **4.3**). Doublets (J = 5.9 Hz) at 7.23 and 5.73 ppm respectively in the ^{1}H-NMR spectrum and peaks at 146.72 (C3) and 129.14 ppm (C2) in the ^{13}C-NMR spectrum clearly pointed towards the installation of the conjugated double bond. A second, less polar product, the brominated indenone **193**, was also recovered as a minor side product in 6% yield along with a small quantity of starting material.



190 **83** **193**

Scheme 4.3

We did not foresee any difficulties for the Diels-Alder reaction on introduction of the aromatic methyl into the indenone, and cycloadduct **194** was indeed obtained in good yield, with the same high regio- and endoselectivity as before *i.e.* 100% (Scheme **4.4**).



83 **136** **194**

Scheme 4.4

SECTION 4.2 Hemi-acetal Based Strategy

Our inability to protect the lactone carbonyl (Chapter 3) forced us to devise a new strategy which would prevent carbonyl ylide formation during the critical arene cyclopropanation step. With our new approach, we envisaged reduction of the lactone to the hemi-acetal once the tetrahydrofuran moiety had been introduced. The ether bridge was expected to ensure that the hemi-acetal ring would remain intact after reduction, despite considerable strain in the cyclic system.

Preferably, the newly formed hydroxyl should be protected as a silyl ether (Figure **4.3**), as this masking group has been particularly effective in preventing interaction with carbenoid species in other syntheses.[39] A bulky protecting group, such as TIPS,[88] might also be expected to direct the diazoketone side chain towards the aromatic ring.

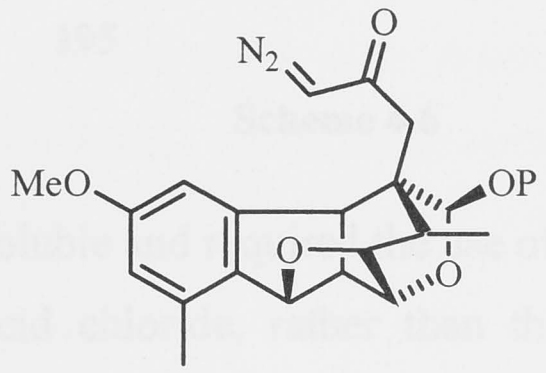
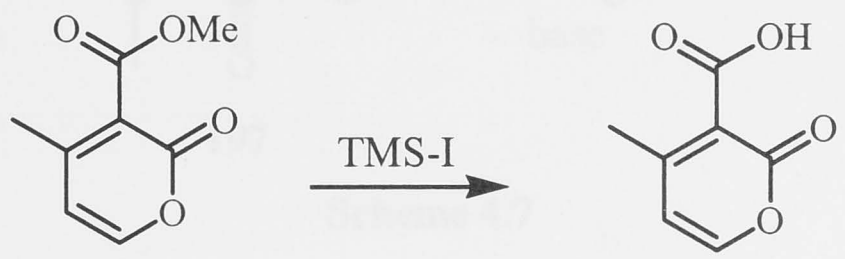


Figure 4.3

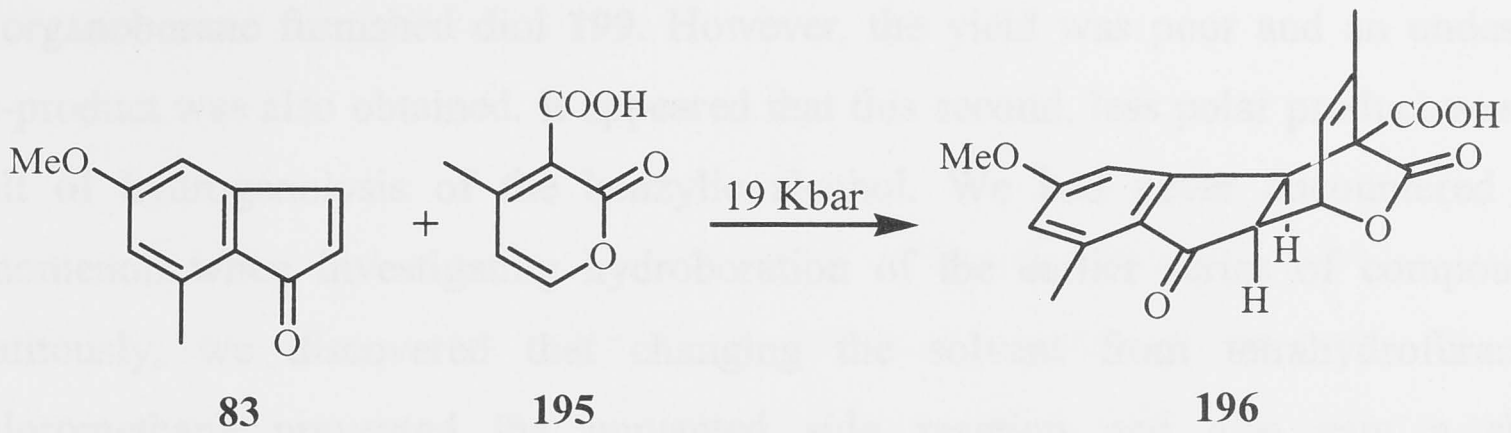
It also appeared to be an opportune time to investigate the influence of the carboxy ester group on the low-yielding hydroboration and oxidation steps. At the very least, demethylation of the pyrone prior to the Diels-Alder reaction would increase the overall degree of convergence in the synthetic scheme. Accordingly, methyl ester **136** was converted to acid **195**, by *in situ* generation of trimethylsilyl iodide, in 75% yield (Scheme **4.5**). Demethylation was apparent from the loss of the methoxy peak at 3.91 ppm in the proton spectrum.



136 **195**

Scheme 4.5

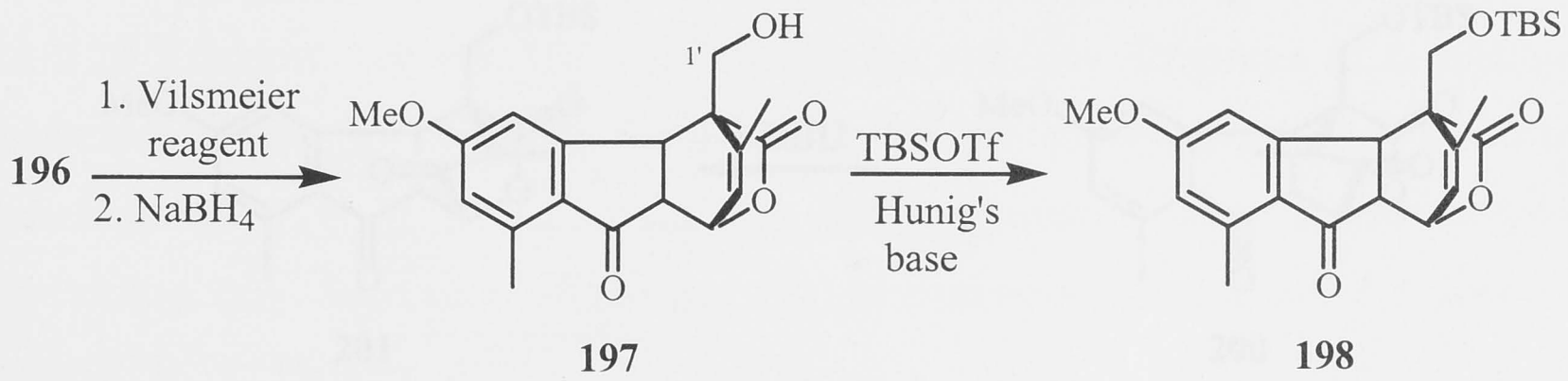
When a mixture of pyrone **195** with indenone **83** were subjected to high pressure for 16 hours, cycloadduct **196** was obtained in 68% (Scheme **4.6**). The carboxylic carbon gave rise to a peak at 171.74 ppm in the ^{13}C-NMR and was corroborated by a broad band in the IR centered on 3430 cm^{-1}.



83 **195** **196**

Scheme 4.6

Acid **196** was particularly insoluble and required the use of THF as the reaction medium for the conversion to the acid chloride, rather than the standard benzene solution (Scheme **4.7**). Reduction with sodium borohydride furnished carbinol **197** in 66% yield. The methylene protons were rendered as doublets at 4.45 and 4.19 ppm with a geminal coupling of 12.2 Hz. C1' was characterised by a peak at 59.42 ppm. Surprisingly, while the olefinic methyl was shifted upfield from 1.56 to 1.38 ppm as might be expected on reduction of the highly electron withdrawing carboxylic acid, the olefinic methine proton was shifted downfield from 5.85 to 6.04 ppm.



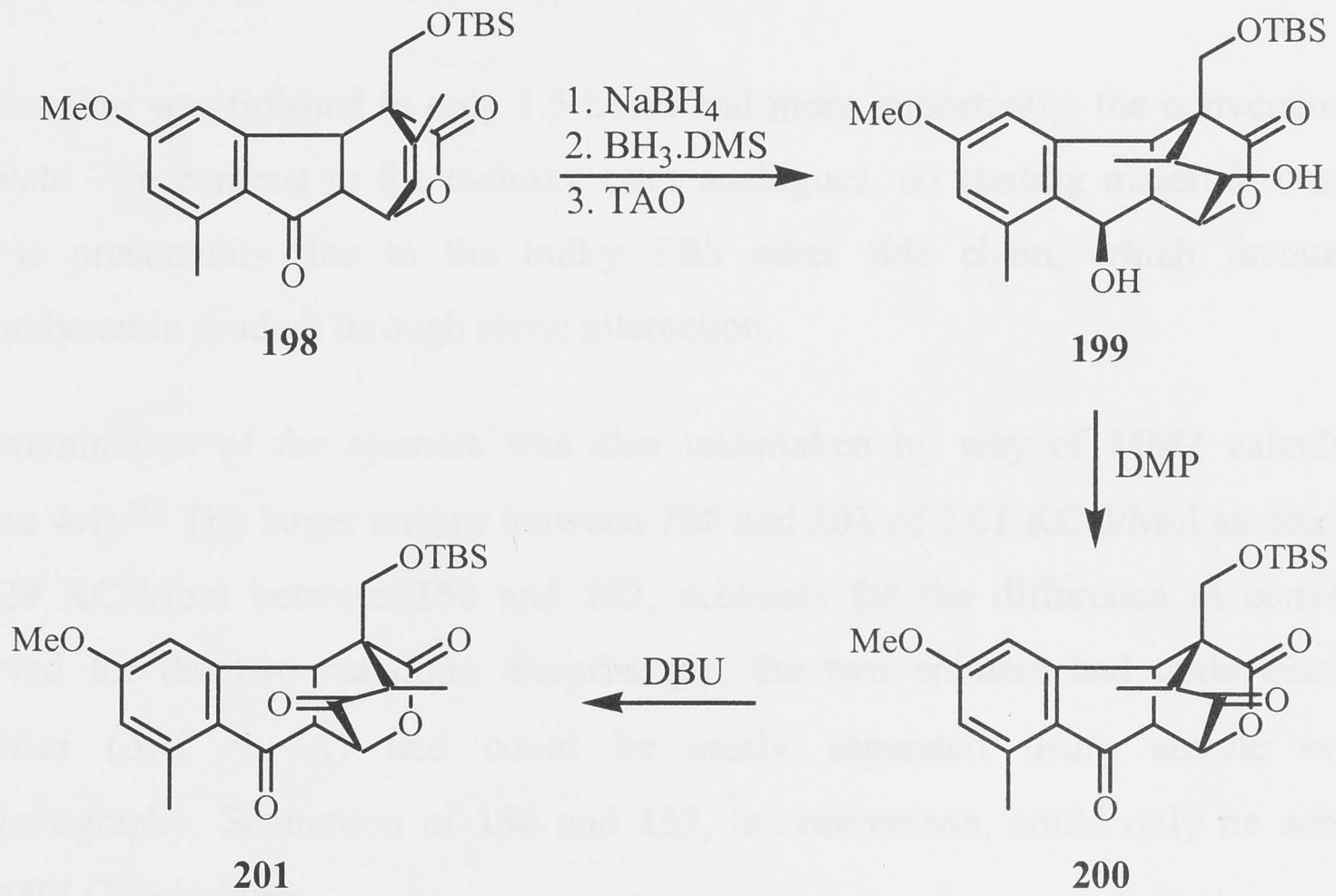
197 **198**

Scheme 4.7

Transformation of **197** into **198** did not proceed as smoothly as expected. In general, primary alcohols are reactive and will form the silyl ether on treatment with *tert.*-butyldimethylsilyl chloride in the presence of a suitable base (e.g. imidazole).[89] For more hindered carbinols, using DMF as the reaction medium provides good results.[90] However, even when a large excess of reagent in a DMF solution was employed, no product was formed. Thus, protection of **197** required use of the triflate[91] and **198** was obtained accordingly in 83% yield.

Simultaneous reduction of the benzylic ketone and the alkene bond with borane was attempted, but it was particularly difficult to determine if the reaction had proceeded to completion by TLC. For that reason, **198** was initially reduced with sodium borohydride in methanol to afford the benzylic alcohol in 89% yield (Scheme **4.8**). Treatment of this product with borane-dimethyl sulfide followed by oxidation with triethylamine oxide of

the organoborane furnished diol **199**. However, the yield was poor and an undesired side-product was also obtained. It appeared that this second, less polar product was the result of hydrogenolysis of the benzylic alcohol. We had never encountered this phenomenon when investigating hydroboration of the earlier series of compounds. Fortuitously, we discovered that changing the solvent from tetrahydrofuran to dichloromethane prevented the unwanted side reaction and also saw a slight improvement in yield to 38%, although this still represented a reduction in comparison to the carboxy ester compounds.



198 **199** **200** **201**

Scheme 4.8

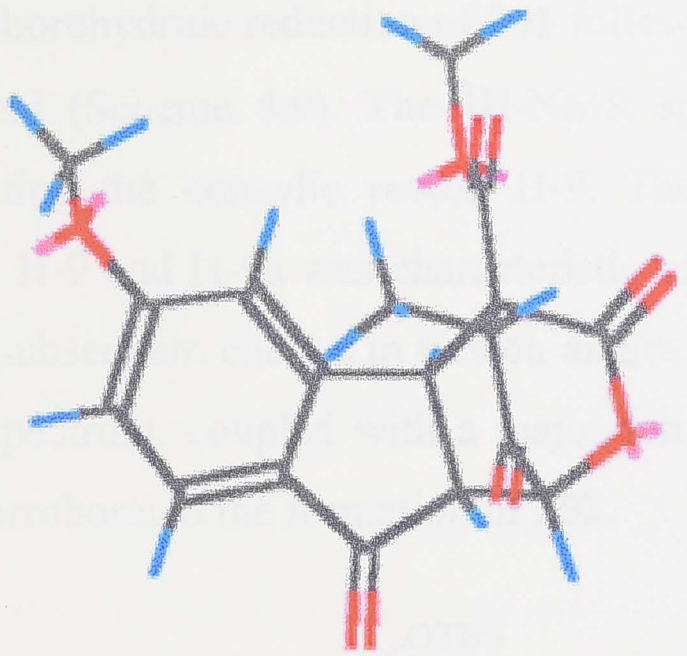
Attempted oxidation of the diol with the Dess-Martin periodinane, precomplexed with *tert.*-butyl alcohol, afforded **200** in mediocre yield (34%). In contrast to the carboxy ester series, it was found that the precomplexing procedure actually decreased the yield of the diketone. In particular, the $NaHCO_3/Na_2S_2O_3$ hydrolysis resulted in a cloudy solution. Oxidation with the Dess-Martin reagent neat in tetrahydrofuran over 16 hours produced **200** in 58% yield. Quaternary carbons at 204.53 (C11) and 197.98 ppm (C9) in the ^{13}C-NMR confirmed the conversion to the diketone. A major ion of *m/z* 387 in the mass spectrum represented loss of a *tert.*-butyl group from the silyl protecting group.

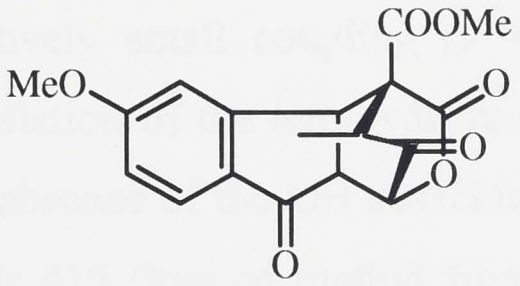
SECTION 4.3 Epimerisation

Treatment of **200** with a catalytic amount of DBU afforded epimer **201** in 98% yield *via* the enolate intermediate. Once again, this transformation was manifest in the ^{1}H-NMR spectrum. The bridge methyl shifted downfield from 0.45 to 0.98 ppm as it moved out of the influence of the aromatic ring and adopted the *exo*-stereochemistry. Conversely, the methine proton was shifted upfield by 0.70 ppm to 1.83 ppm as a result of shielding by the π electrons of the benzene ring.

The reaction was finished in only 1.5 hours and more importantly, the conversion was complete – in contrast to the carboxy ester analogues, no starting material remained. This is presumably due to the bulky TBS ether side chain, which favours the thermodynamic product through steric interaction.

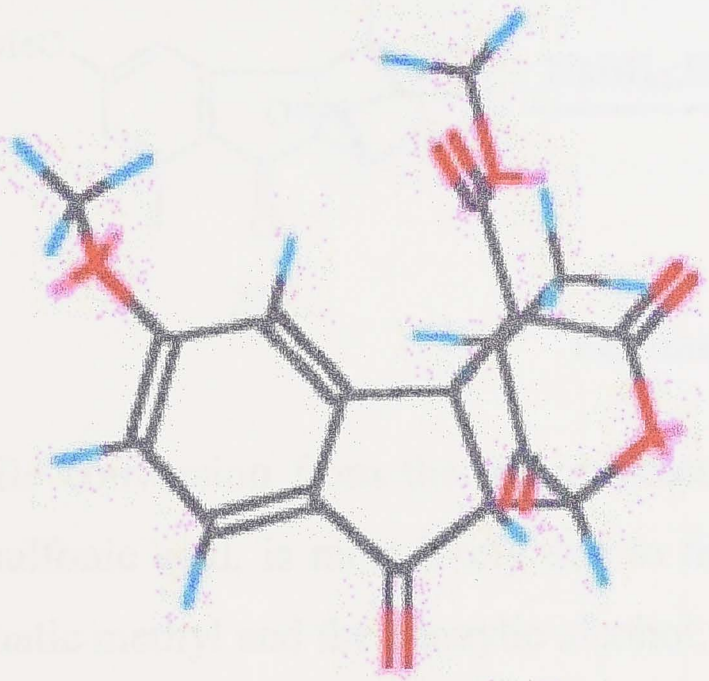
An examination of the epimers was also undertaken by way of MM2 calculations (Figure **4.4**).[92] The larger energy between **200** and **201** of 2.01 KCal/Mol as compared to 0.29 KCal/mol between **150** and **152**, accounts for the difference in conversion observed for the two reactions. Surprisingly, the two epimers had quite dissimilar polarities (ΔRf = 0.1) and could be easily separated using simple column chromatography. Separation of **150** and **152**, in comparison, could only be achieved with MPLC techniques.

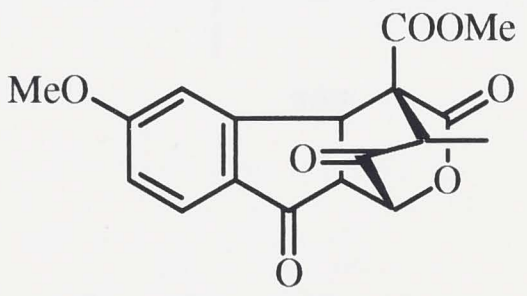




150

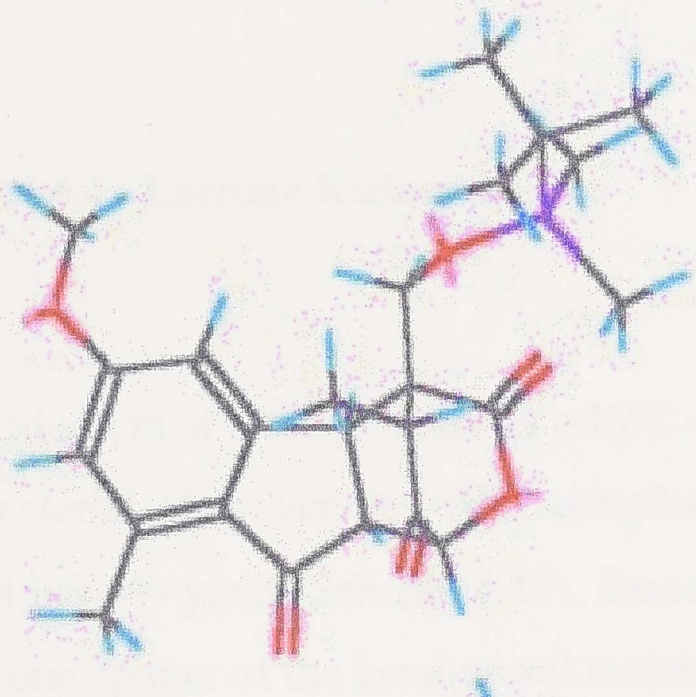
MM2 ENERGY 50.27 KCal mol^{-1}

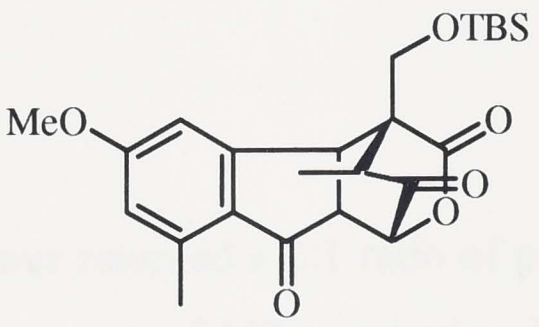




152

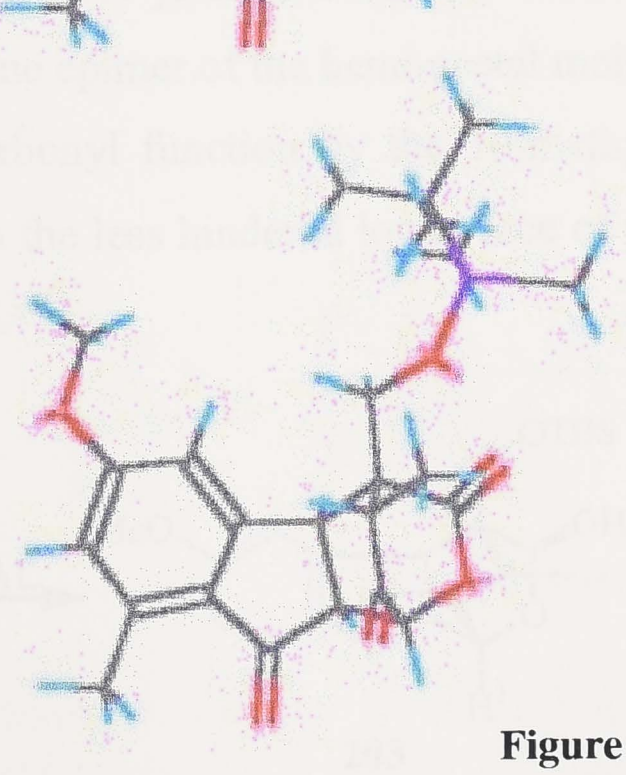
MM2 ENERGY 49.98 KCal mol^{-1}

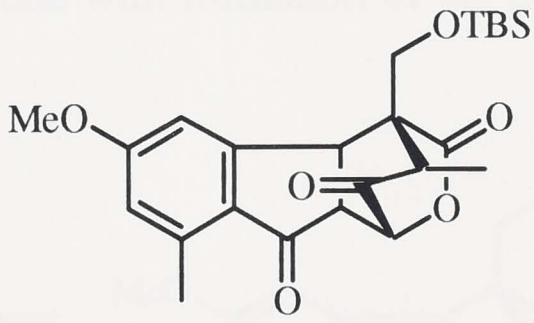




200

MM2 ENERGY 47.09 KCal mol^{-1}



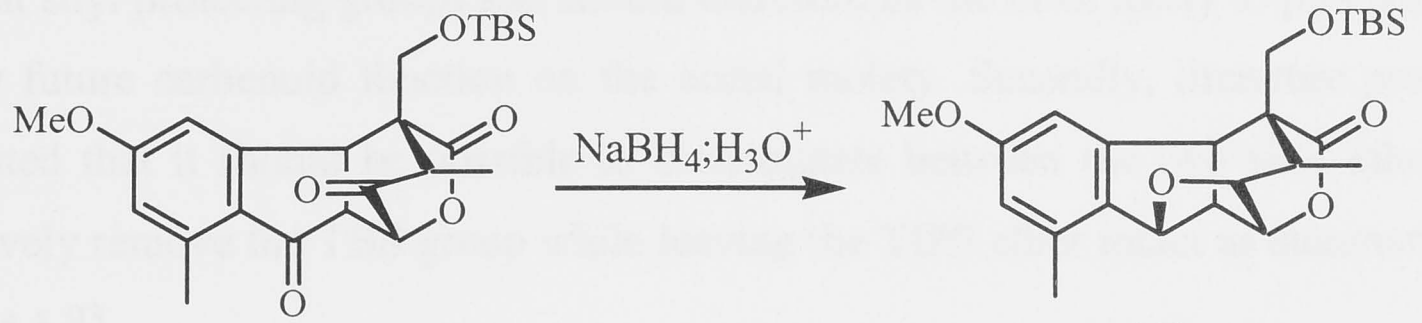


201

MM2 ENERGY 45.08 KCal mol^{-1}

Figure 4.4

Sodium borohydride reduction of **201** followed by acidic work-up afforded ether **202** in 64% yield (Scheme **4.9**). The ^{1}H-NMR spectrum displayed a doublet at 5.30 ppm representing the benzylic proton H-9. The relatively small coupling (J = 5.5 Hz) between H-9 and H-9a was characteristic of installation of the tetrahydrofuran moiety and the subsequent change in torsion angles. The absence of the OH stretching band in the IR spectrum, coupled with a major ion at *m/z* 415 (loss of methyl from the silyl ether) corroborated the formation of **202**.



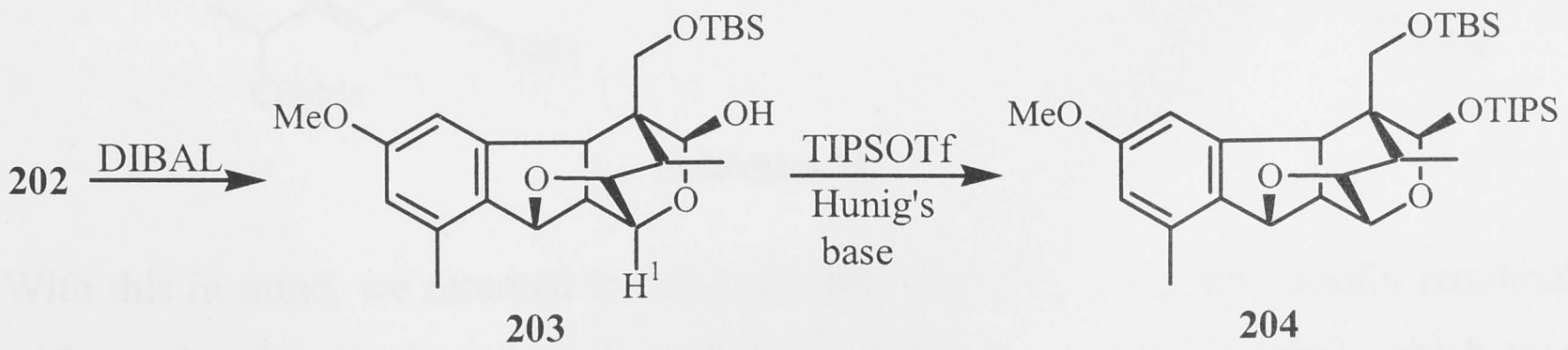
201 **202**

Scheme 4.9

The facile conversion from the intermediate diol to the ether without recourse to *p*-toluenesulfonic acid, is most likely due to the unfavourable steric interaction between the aromatic methyl and the benzylic alcohol, which is relieved on formation of **202**.

SECTION 4.4 Lactone Reduction

DIBAL reduction at a temperature of –50°C or lower returned a 2:1 ratio of product to starting material. However, at –40°C, complete conversion of **202** occurred and **203** was recovered in 66% yield (Scheme **4.10**). Examination of the ^{1}H-NMR spectrum showed that only one epimer of the hemi-acetal moiety had been formed – steric shielding of the lactone carbonyl function by the 10-methyl group ensures approach of the reducing agent from the less hindered lower face of the lactone with formation of the β-hydroxy compound.



203 **204**

Scheme 4.10

The clearest indicators for reduction of the lactone was the upfield shift of H-1 from 5.06 to 4.56 ppm and the appearance of a singlet at 5.30 ppm in the ^{1}H-NMR spectrum.

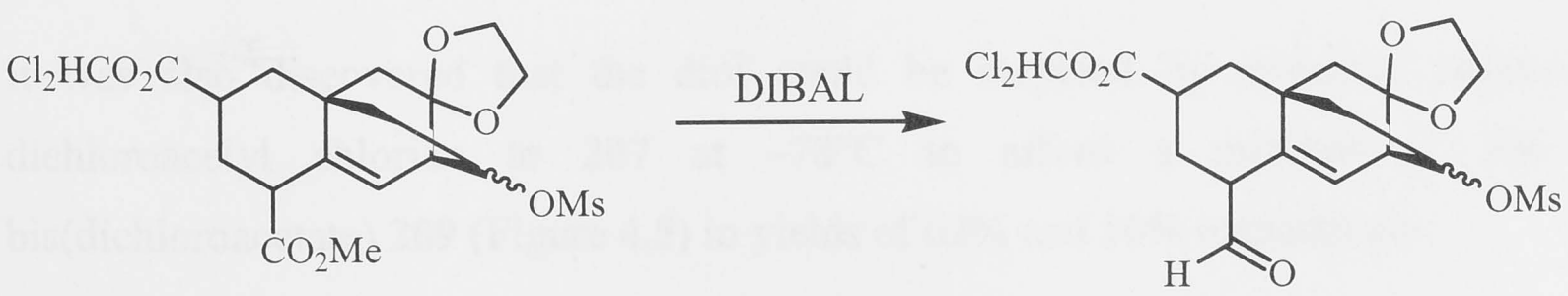
Protection of the free hydroxyl as a TIPS ether required a large excess (8 eq) of triisopropylsilyl triflate. **204** was recovered in 45% yield and was characterised by a multiplet centered on 1.04 ppm in the proton spectrum.

The TIPS protecting group was chosen for two main reasons. First, it is one of the bulkiest silyl protecting groups and should therefore be the most likely to prevent attack of any future carbenoid function on the acetal moiety. Secondly, literature precedent suggested that it should be possible to discriminate between the two silyl ethers and selectively remove the TBS group while leaving the TIPS ether intact as summarised in Table **4.1**.[93]

Half-life of R_3SiOR^* Under Desilylation Conditions					
$R^* = n$-butyl			R^* = cyclohexyl		
R^3	H^+	OH^-	H^+	OH^-	F^-
TBDM	< 1 min	1 h	< 4 min	26 h	76 min
TIP	18 min	14 h	100 min	44 h	137 min
TBDP	244 min	< 4 h	360 min	14 h	-

Table 4.1

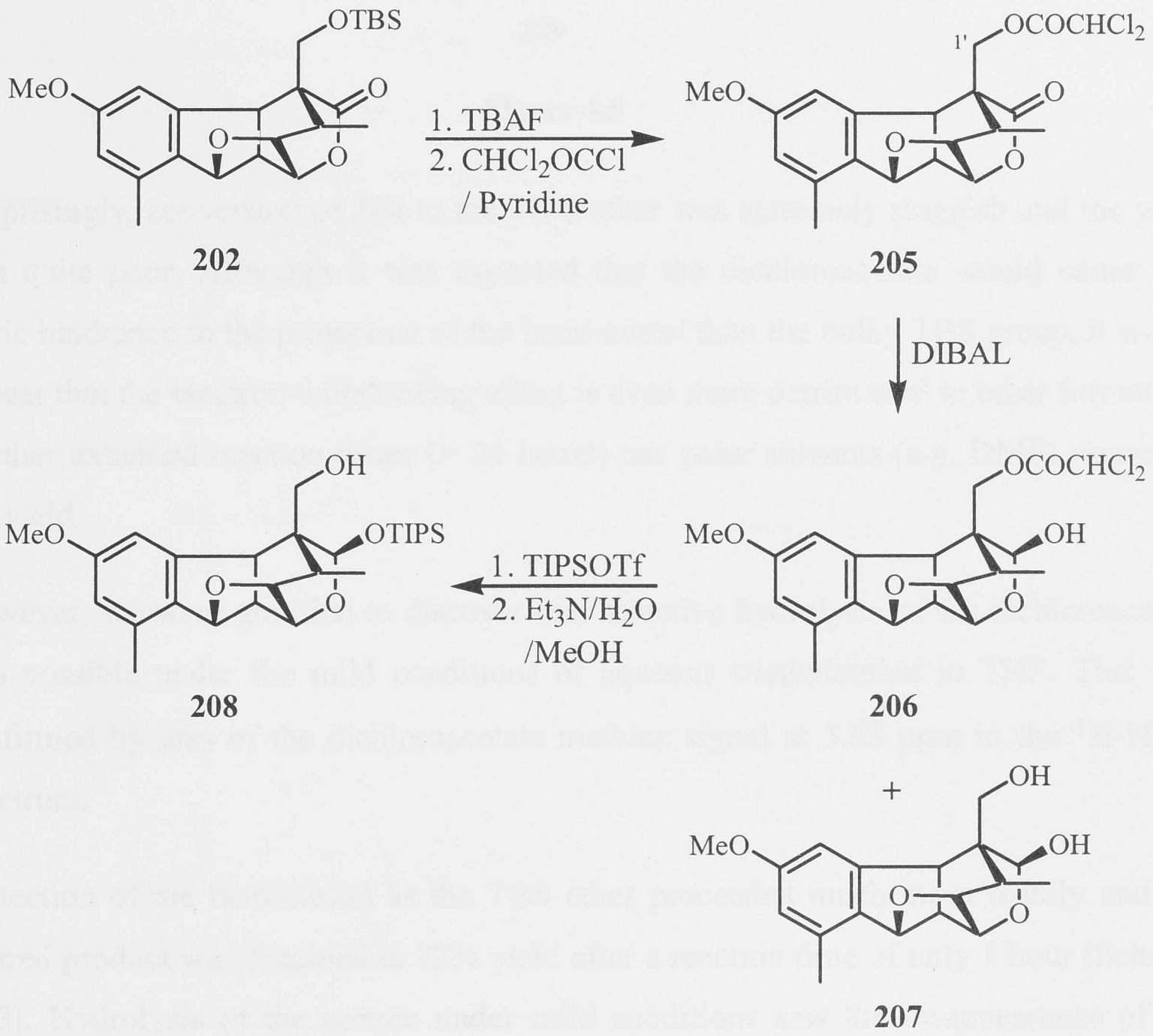
Unfortunately, we were unable to discriminate between the two masking groups under a wide range of conditions – either both groups remained intact or both were cleaved simultaneously. However, earlier work on gibberellin intermediates by Chiu demonstrated that a DIBAL reduction could be conducted in the presence of a dichloroacetate protecting group (Scheme **4.11**).[94]



Scheme 4.11

With this in mind, we returned to substrate **202**. The TBS ether was readily removed with tetrabutylammonium fluoride in THF to afford the primary alcohol, which was

reprotected as the dichloroacetate **205** in 96% yield (Scheme **4.12**). The acetate methine proton appeared as a singlet at 6.09 ppm and was accompanied by a downfield shift of the methylene protons attached to C1'.

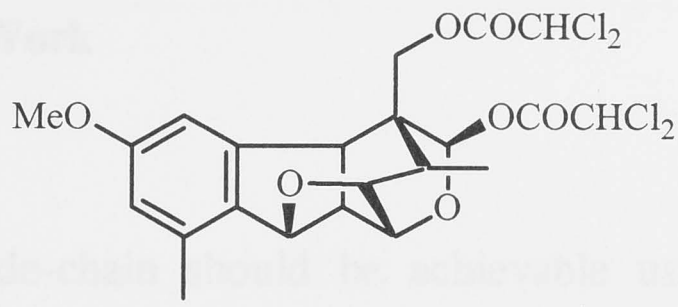


208 **206** **207**

Scheme 4.12

Reduction of **205** with DIBAL at –40°C afforded the desired hemi-acetal **206** in 57% yield, along with diol **207** (18%). Once again, a singlet at 5.29 ppm and an upfield shift of H-1 from 5.11 to 4.56 ppm was apparent in the proton spectrum. The loss of the quaternary signal at 172.09 ppm and the appearance of the hemi-acetal carbon at 91.14 ppm also confirmed the reduction of the lactone.

It was also discovered that the diol could be recycled by dropwise addition of dichloroacetyl chloride to **207** at –78°C to afford a mixture of **206** and bis(dichloroacetate) **209** (Figure **4.5**) in yields of 62% and 10% respectively.



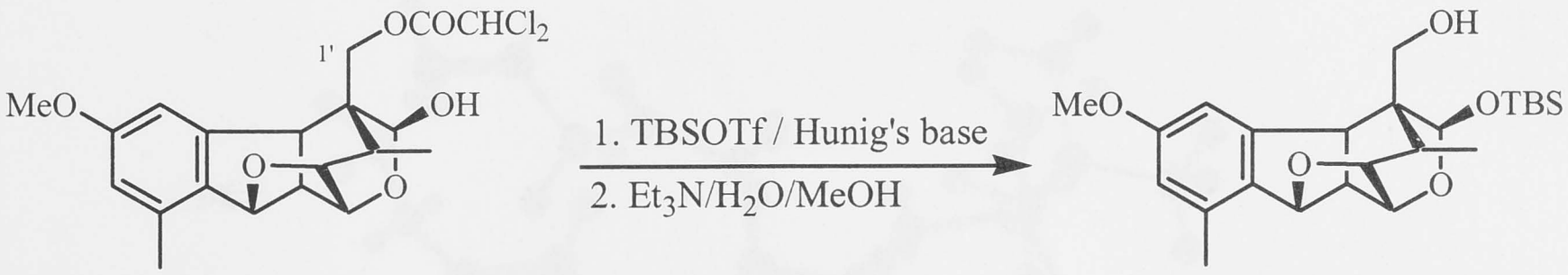
209

Figure 4.5

Surprisingly, conversion of **206** to the TIPS ether was extremely sluggish and the yield was quite poor. Although it was expected that the dichloroacetate would cause less steric hindrance to the protection of the hemi-acetal than the bulky TBS group, it would appear that the electron-withdrawing effect is even more detrimental to ether formation. Neither extended reaction times (> 24 hours) nor polar solvents (e.g. DMF) improved the yield.

However, we were gratified to discover that selective hydrolysis of the dichloroacetate was possible under the mild conditions of aqueous triethylamine in THF. This was confirmed by loss of the dichloroacetate methine signal at 5.88 ppm in the ^{1}H-NMR spectrum.

Protection of the hemi-acetal as the TBS ether proceeded much more readily and the desired product was obtained in 72% yield after a reaction time of only 1 hour (Scheme **4.13**). Hydrolysis of the acetate under mild conditions saw the disappearance of the chloroacetate signal at 5.91 ppm accompanied by an upfield shift of the C1' methylene protons to 3.44 and 2.95 ppm. The conversion was also evident in the ^{13}C-NMR with the loss of the acetate carbonyl resonance at 164.20 ppm. Moreover, the deprotection was also confirmed in the mass spectrum with a molecular ion at *m/z* 432.

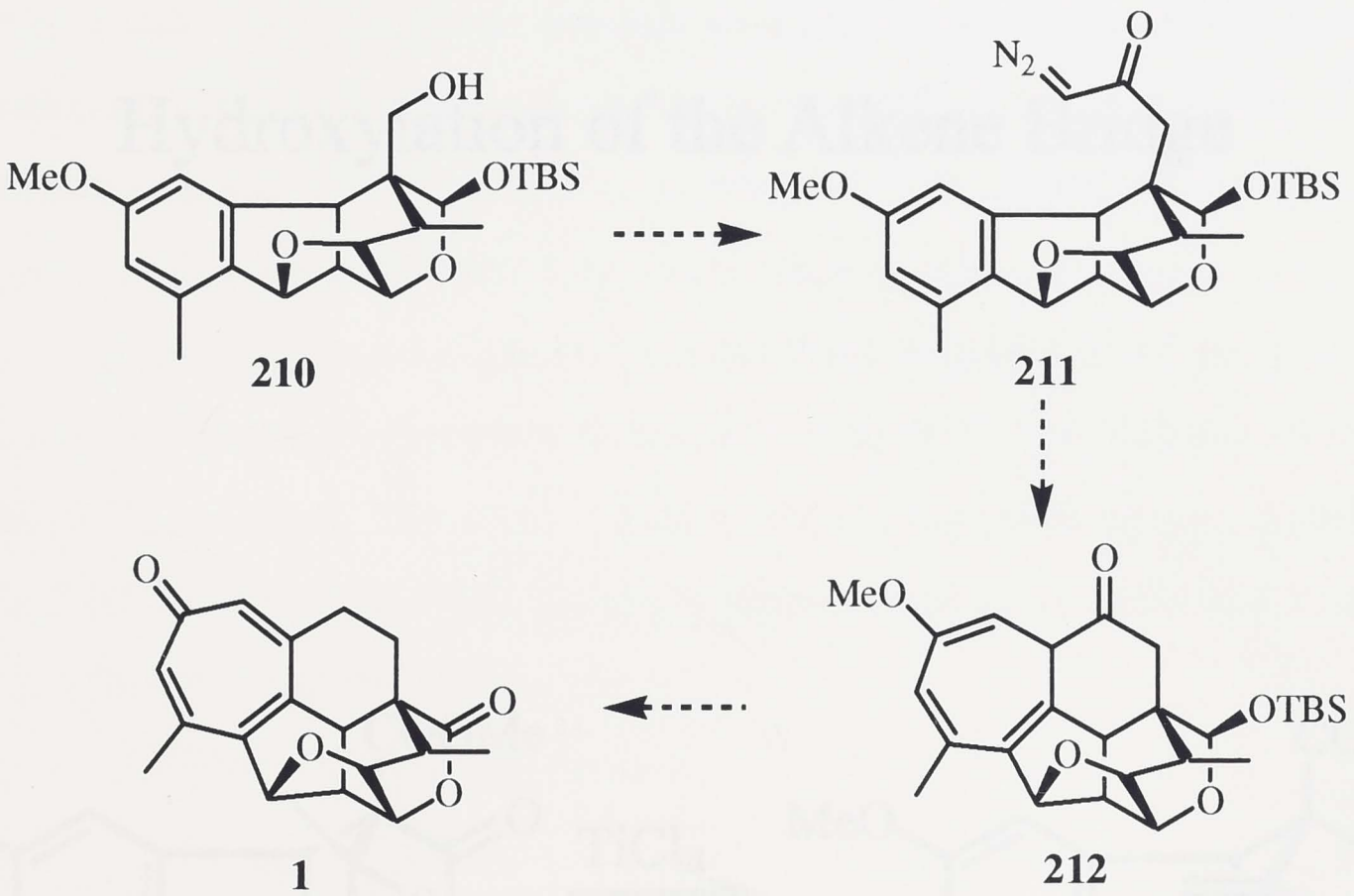


206 **210**

Scheme 4.13

SECTION 4.5 Future Work

Homologation of the side-chain should be achievable using the Wittig chemistry employed in the earlier series. After formation of the α-diazoketone and subsequent cyclopropanation, it should be possible to delete the superfluous carbonyl function by reduction to the alcohol and elimination via the tropylium ion.[45] Removal of the TBS protecting group and oxidation to the lactone is expected to afford the target molecule **1**.



Scheme 4.14

The sheer size of the silyl ether is expected to shield the neighbouring acetal CH bond against insertion reactions and to retard attack by the ether oxygen atoms on the carbenoid intermediate (Figure **4.6**).

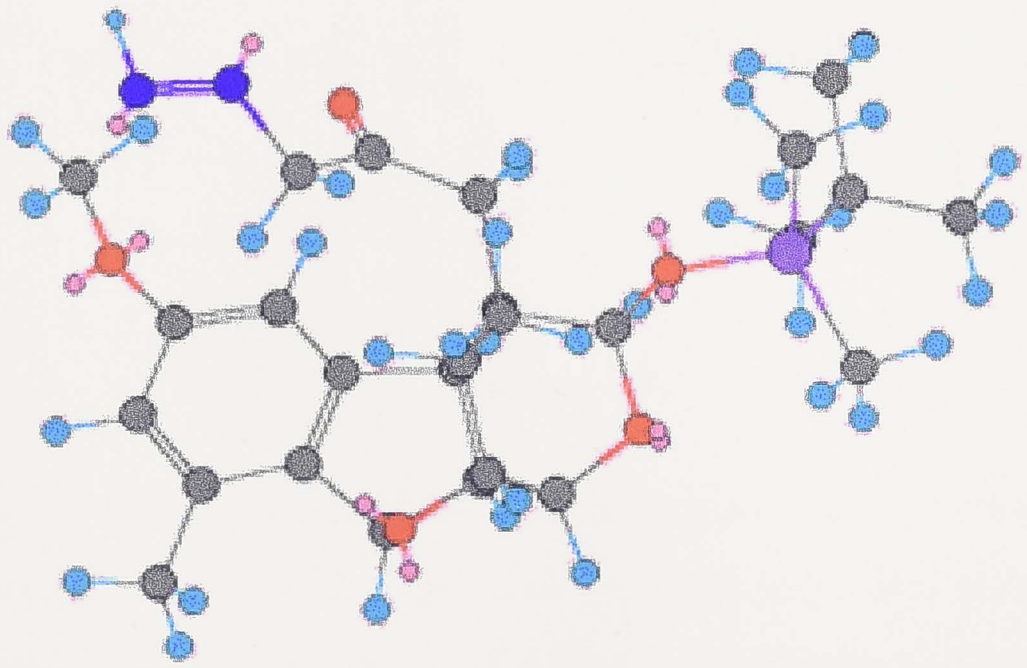
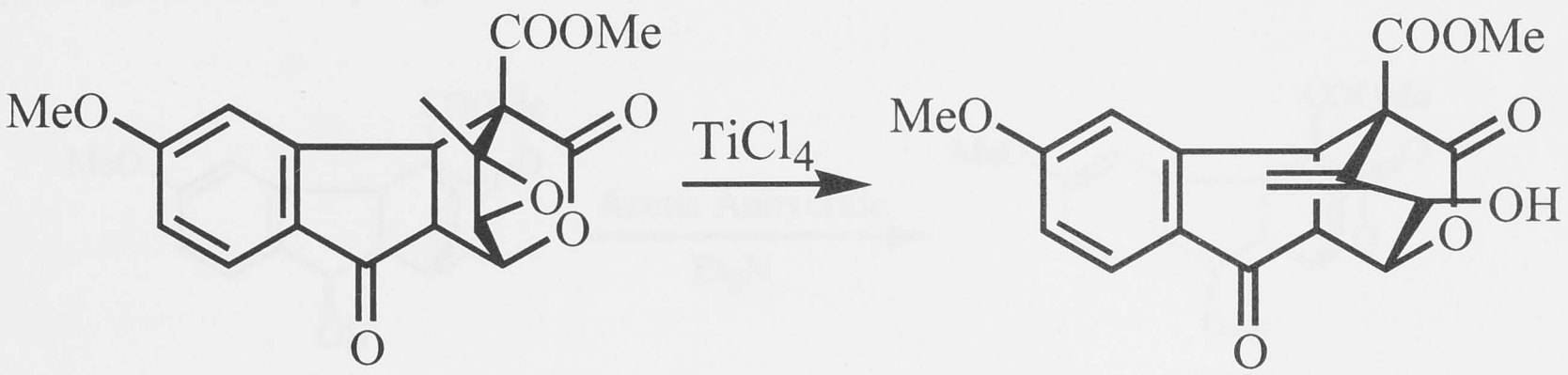


Figure 4.6

Chapter Five

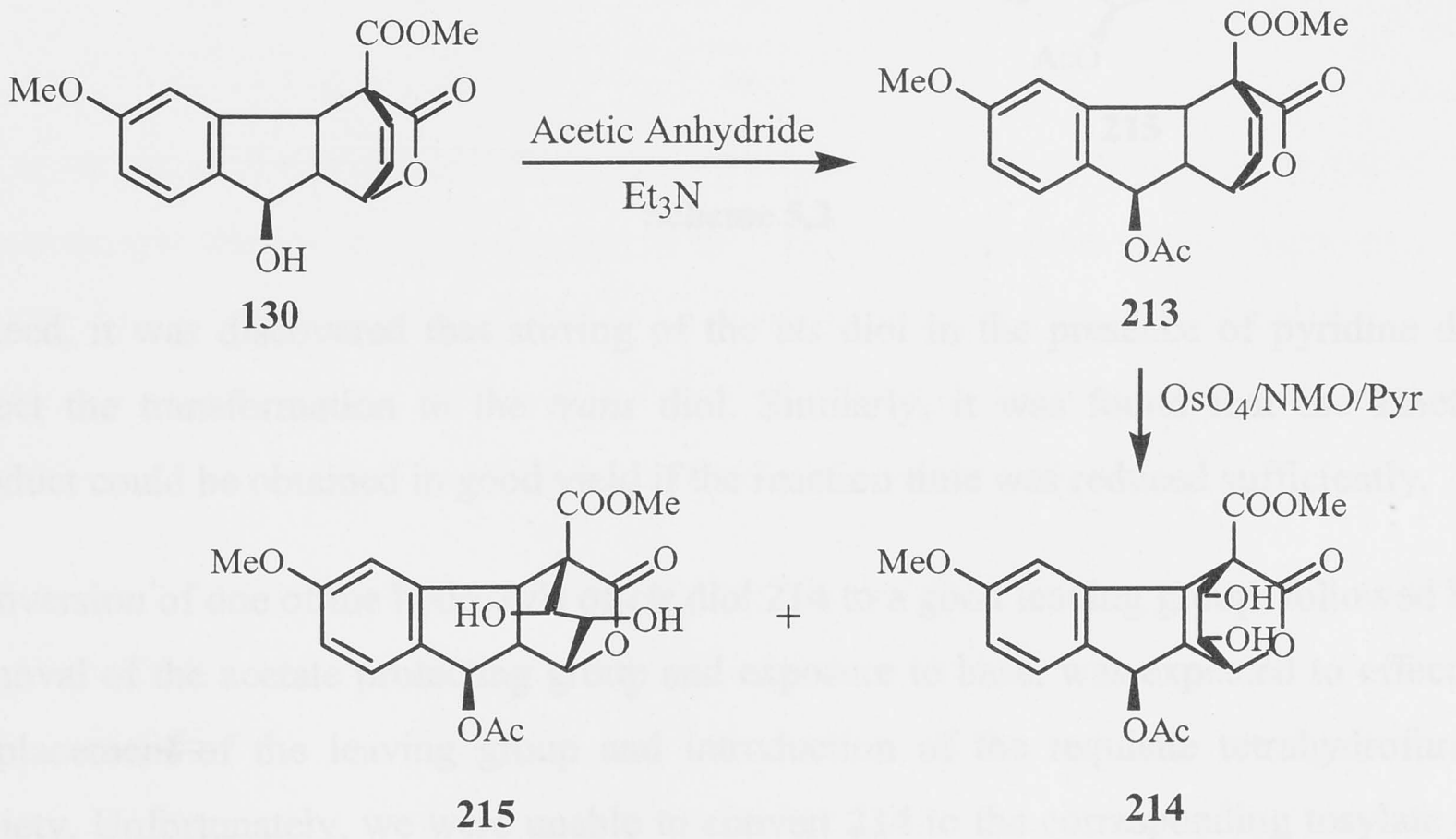
Hydroxylation of the Alkene Bridge



SECTION 5.1 Dihydroxylation

The cycloadduct alkene bond had previously proven to be exceptionally unreactive, resulting in poor yields for the hydroboration and oxidation steps. There was also the outright failure to effect the mercury-mediated cyclopropyl ring opening. We therefore decided to investigate a number of different routes to functionalising the olefinic bond, primarily with the aim of introducing oxygen and establishing the ether linkage.

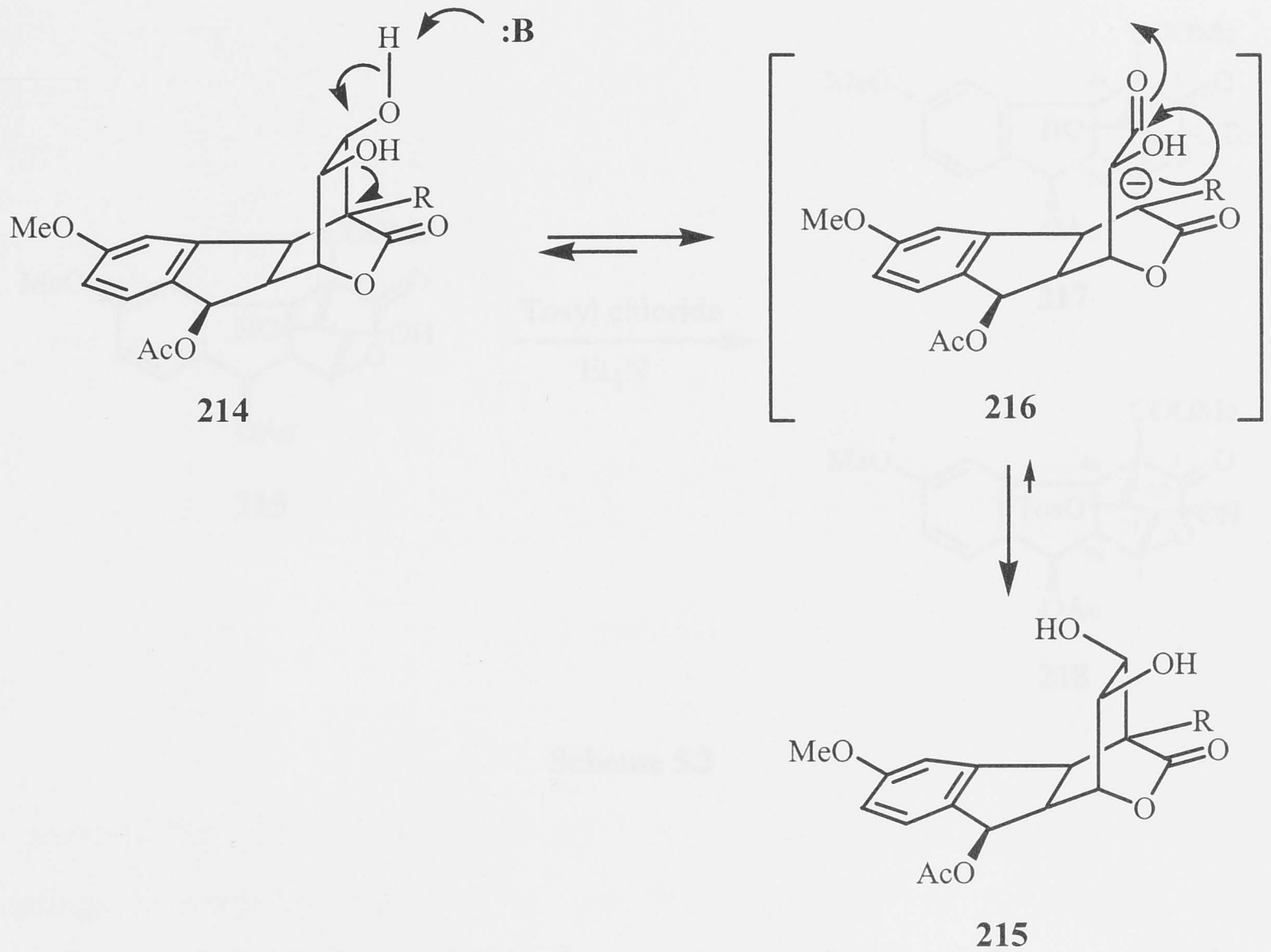
Our first approach was based on an osmium tetroxide mediated dihydroxylation.[95] The benzylic alcohol **130** was first protected as the acetate **213** in excellent yield (97%), then treated with a catalytic amount of OsO_4, regenerated with *N*-methylmorpholine oxide, in the presence of pyridine (Scheme **5.1**). Under such conditions a single product would normally be expected with *syn* addition from the less-hindered side of the double bond. We were suitably surprised, therefore, to find a mixture of two products on examination of the ^{1}H-NMR spectrum. The minor product was characterised by two doublets (J = 7.6 Hz) at 5.00 and 4.69 ppm while the major product showed doublets at 4.17 and 4.00 ppm again with couplings of 7.6 Hz.



Scheme 5.1

It was observed that if the reaction time was increased, then the minor product was completely converted to the major product. Accordingly, the minor product was assigned *cis* diol structure **214** and the major product was assigned *trans* diol structure **215**.

A probable mechanism for the conversion of the *cis* to the *trans* diol is outlined in Scheme **5.2**. Deprotonation of the hydroxyl results in a reverse aldol type reaction. The carbanionic intermediate is stabilised by both the carboxy ester side chain and the lactone ring. As the system is in equilibrium, there is a gradual accumulation of thermodynamic product **215** where the eclipsing of the *cis* hydroxyls is now relieved.

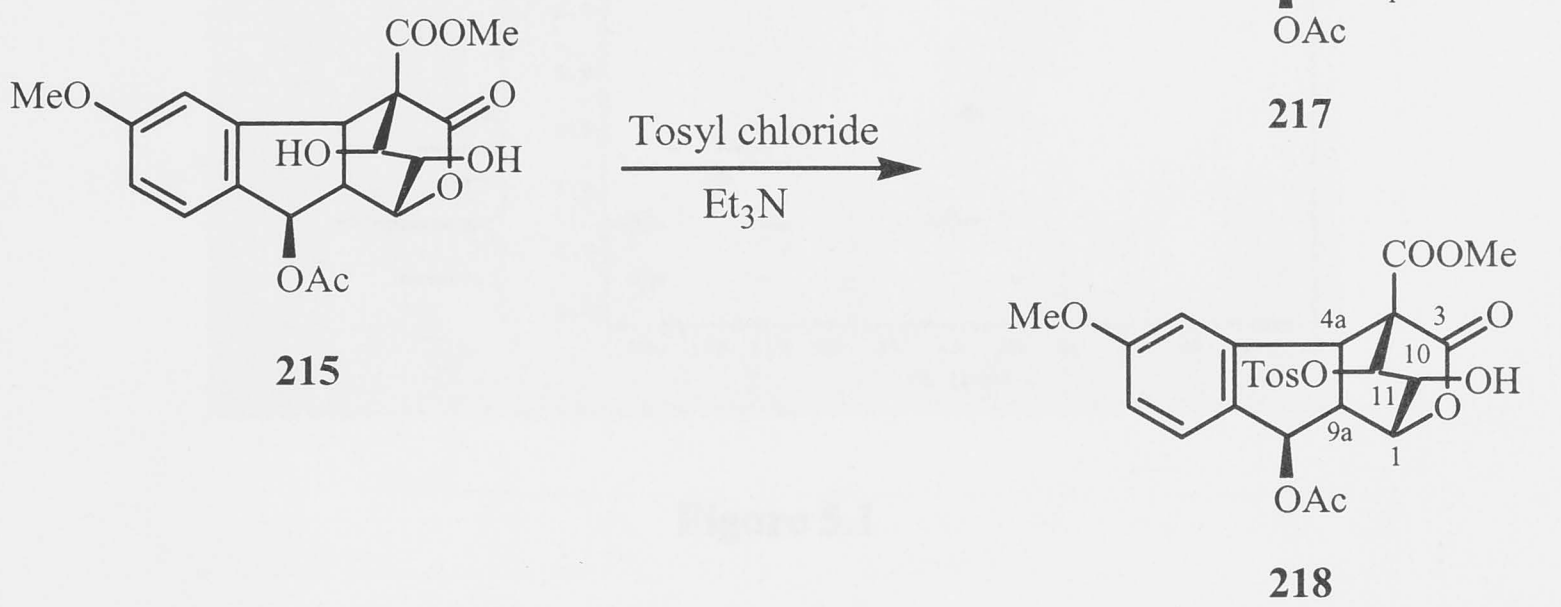


Scheme 5.2

Indeed, it was discovered that stirring of the *cis* diol in the presence of pyridine did effect the transformation to the *trans* diol. Similarly, it was found that the kinetic product could be obtained in good yield if the reaction time was reduced sufficiently.

Conversion of one of the hydroxyls of *cis* diol **214** to a good leaving group, followed by removal of the acetate protecting group and exposure to base, was expected to effect a displacement of the leaving group and introduction of the requisite tetrahydrofuran moiety. Unfortunately, we were unable to convert **214** to the corresponding tosylate or mesylate. This was most likely due to steric hindrance and hydrogen bonding between the two hydroxy groups.

Treatment of *trans* diol **215** with *p*-toluenesulfonyl chloride and triethylamine afforded two products (Scheme **5.3**). The less polar, major product was obtained in 57% yield, while the minor product was recovered in 27% yield. One might expect the *exo* tosylate **217** to be the major product, as the *exo* hydroxyl is less hindered. Similarly, the *exo* tosylate product should be less polar than **218** which has a free *exo* hydroxyl.



Scheme 5.3

In order to definitively establish the structures of the products, a number of spectrometric studies were conducted. In the ^{1}H-NMR spectrum of the major product the two bridge methine protons appear as doublets (J = 3.4 Hz) at 5.09 and 4.40 ppm which, by examining the connectivites from the HMQC spectrum,[96] we found were attached to carbons at 80.55 and 74.34 ppm respectively (Figure **5.1**).

Considering that the tosylate would be expected to shift the adjacent methine downfield, we provisionally assigned structure **217** to the major product.

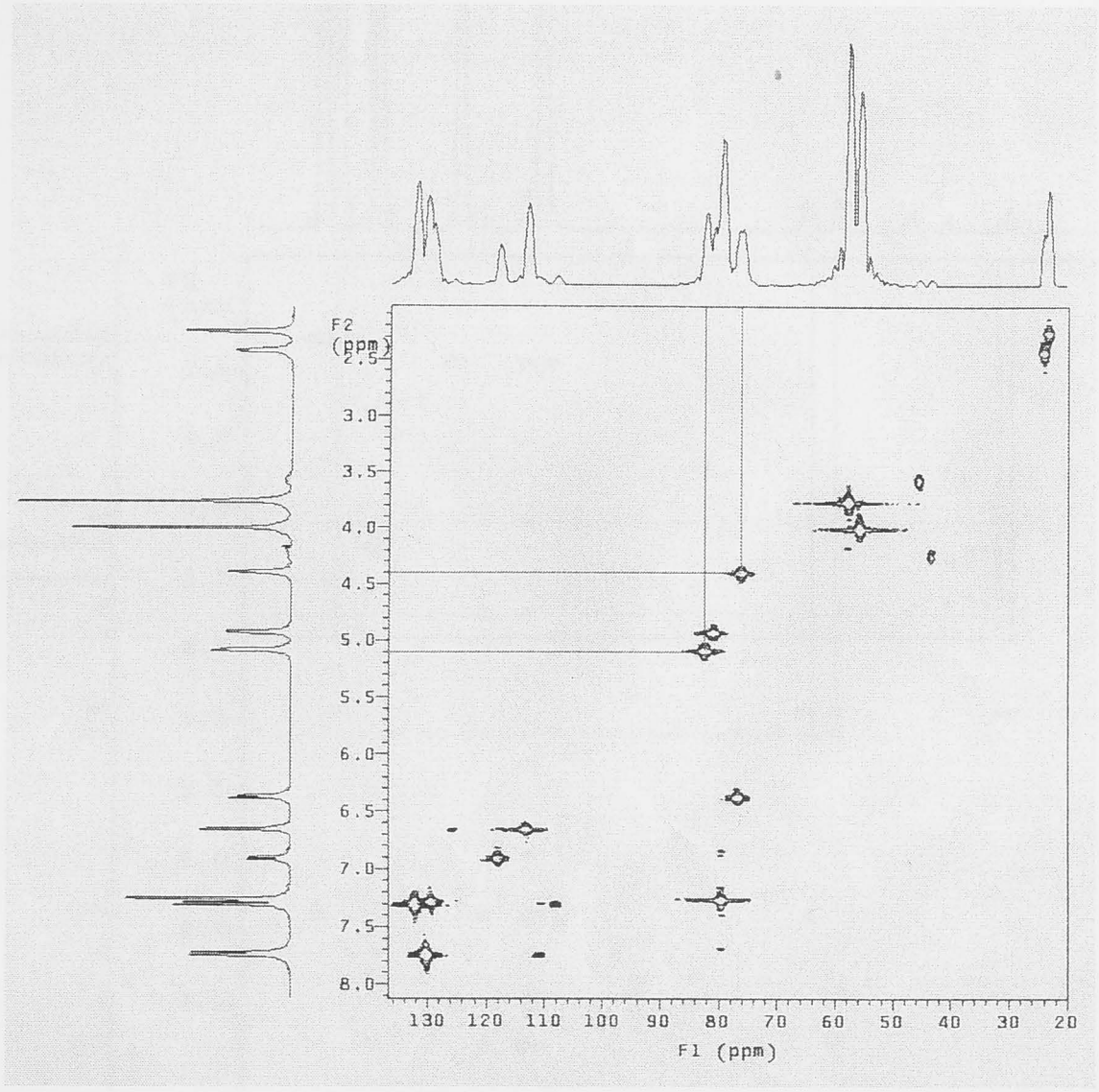


Figure 5.1

To confirm that we have the assumed structure, we should ideally see long-range couplings between H-11→C1→C9a and H-9a→C1→C11 in the HMBC spectrum (Figure **5.2**). While there is a coupling between H-11→C1 (79.14 ppm), the H-11→C9a (43.77 ppm) interaction is absent. H-9a, which is rendered as a double doublet of doublets at 3.57 ppm in the ^{1}H-NMR spectrum, does not display a coupling to C11 either.

However, the couplings for the more upfield methine, H-10, are indeed present. The HMBC spectrum shows an interaction between H-10→C4a (41.64 ppm) and a weak coupling to the lactone carbonyl C3 (168.94 ppm). Similarly, H-4a, rendered as a doublet (J = 10.3 Hz) at 4.23 ppm shows a strong H-4a→C4 (60.71 ppm) →C10 (74.34 ppm) interaction, thus confirming that the assigned structure is indeed correct.

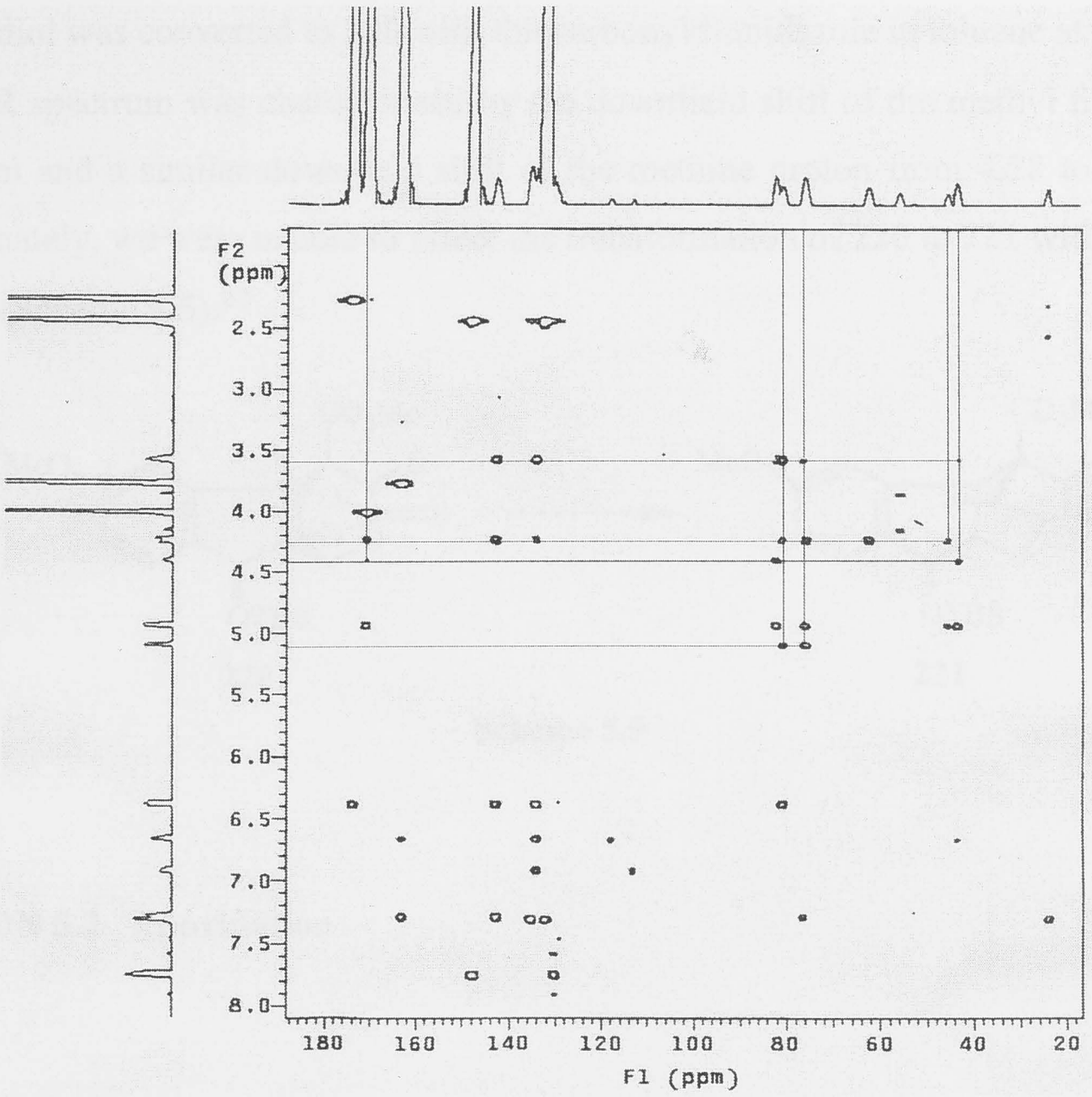
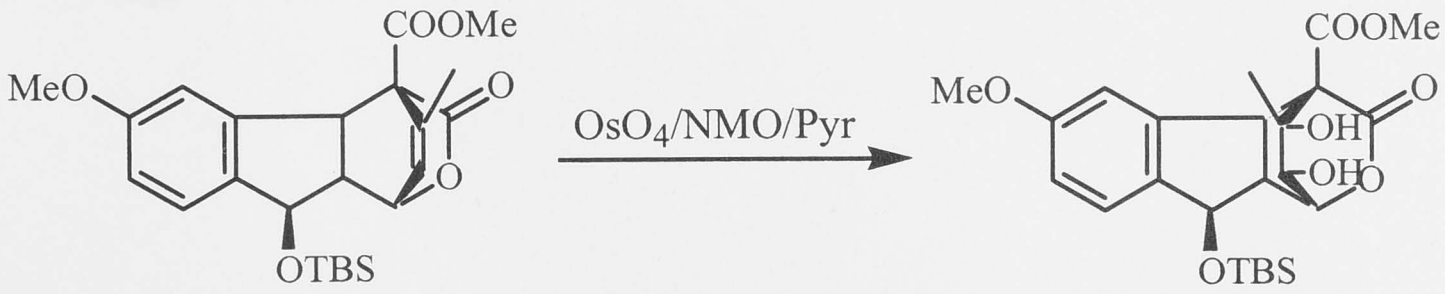


Figure 5.2

When cleavage of the acetate group of the tosylate compounds was attempted, the desired benzylic alcohol was not obtained. Rather, hydroxide attack on the lactone led to unwanted side products.

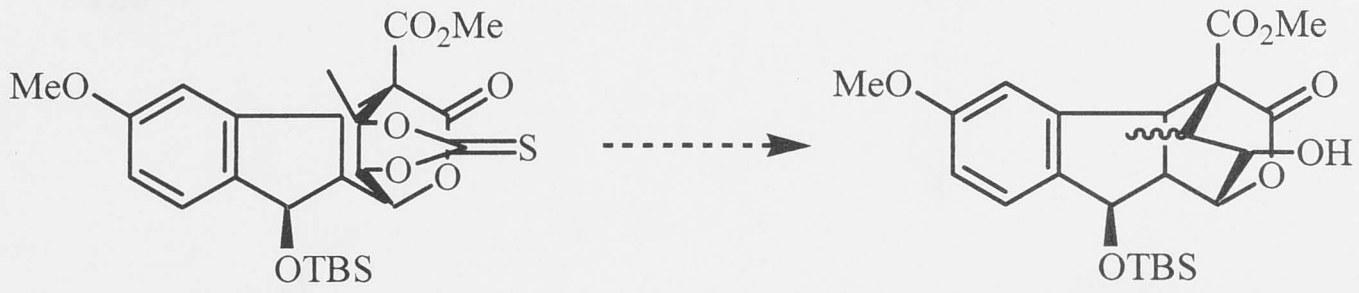
A similar approach was taken with alkene **155** which was converted to *cis* diol **219** in 90% yield (Scheme **5.4**). Only one product was recovered even with extended reaction times. Presumably, the introduction of the methyl at C10 prevents the reverse aldol reaction outlined earlier.



155 **219**

Scheme 5.4

The *cis* diol was converted to **220** with thiocarbonyldiimidazole in toluene at reflux. The ^{1}H-NMR spectrum was characterised by the downfield shift of the methyl from 0.80 to 1.01 ppm and a similar downfield shift of the methine proton from 4.28 to 4.91 ppm. Unfortunately, we were unable to effect the transformation of **220** to **221** with tributyltin hydride (Scheme **5.5**).[97]

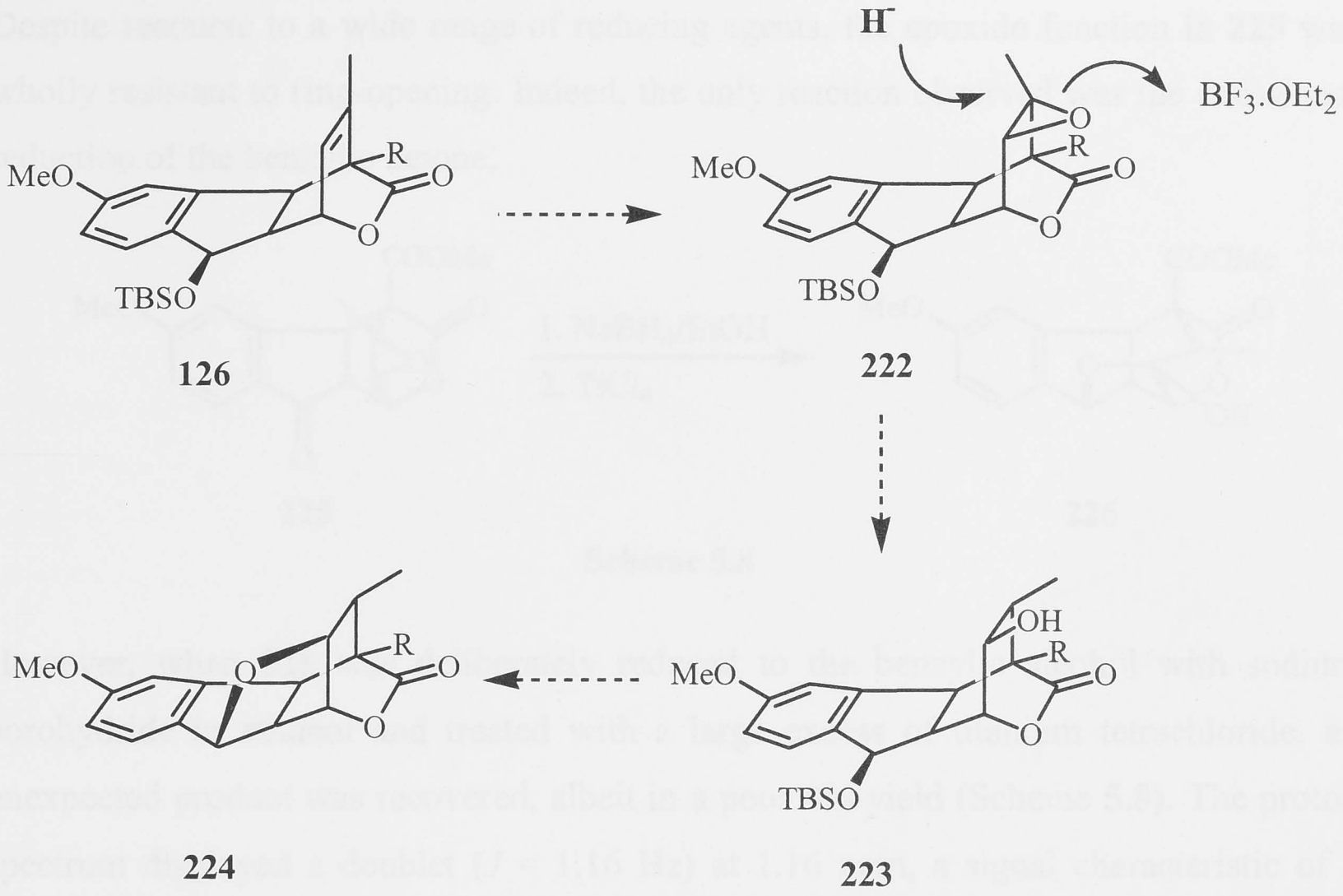


220 **221**

Scheme 5.5

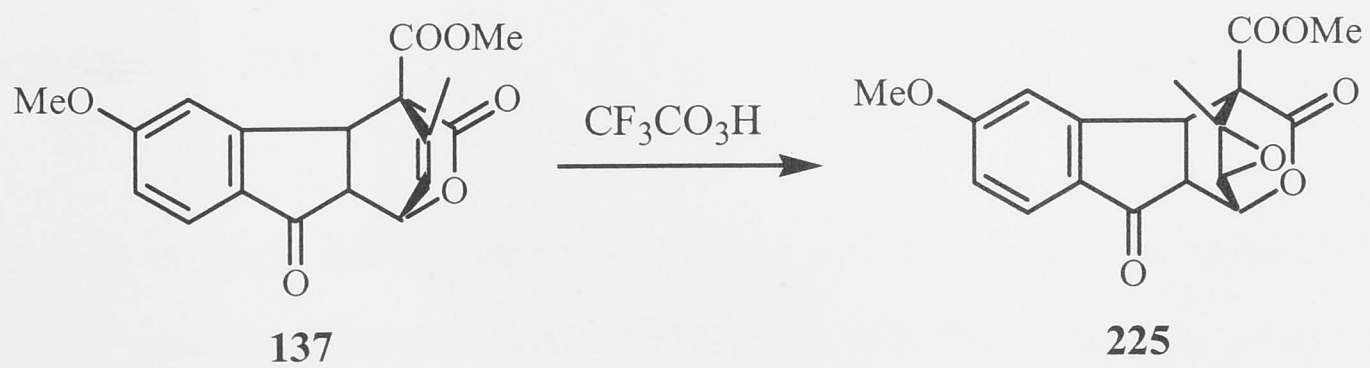
SECTION 5.2 Epoxidation

Epoxidation of the olefinic bond offers an alternative route for the introduction of oxygen. Lewis acid promoted opening of **222** with concomitant hydride delivery to the more highly substituted centre[98] should afford alcohol **223** with the methyl in the *exo* position (Scheme **5.6**). Conversion of the hydroxyl to a good leaving group, followed by deprotection of the benzylic alcohol and treatment with base should then establish the ether bond as per **224**.



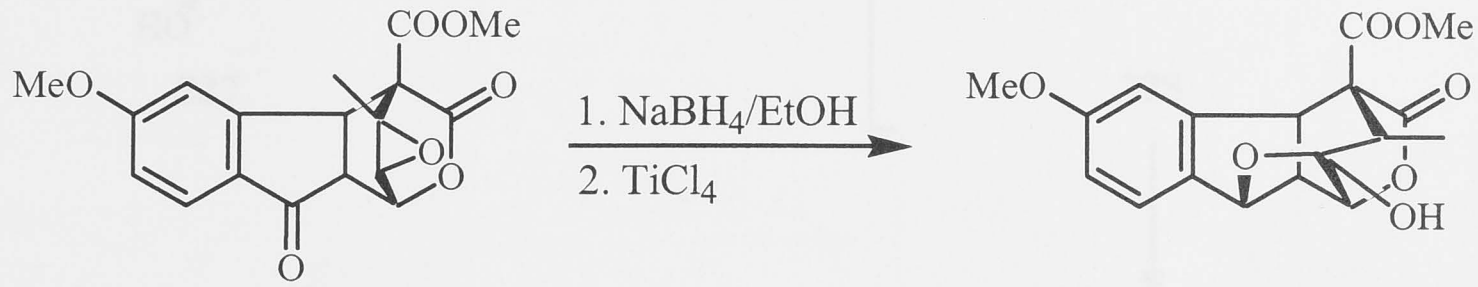
Scheme 5.6

Alkene **126** proved to be particularly unreactive towards epoxidation. Neither *m*-chloroperbenzoic acid,[99] nor dimethyldioxirane,[100] nor methyl(trifluoromethyl) dioxirane,[101] were potent enough to oxidise the double bond. Treatment with trifluoroperacetic acid, generated *in situ* from the standard combination of trifluoroacetic anhydride and urea-hydrogen peroxide (UHP),[102] merely resulted in cleavage of the TBS ether and reoxidation to the benzylic ketone. However, when the above procedure was repeated on **137**, the desired epoxide was obtained, although the yield was poor (~5%) (Scheme **5.7**). Gratifyingly, when sodium percarbonate was substituted for UHP, **225** was afforded in 52% yield.[103] H-11 was rendered as a doublet (J = 3.0 Hz) at 3.68 ppm in the ^{1}H-NMR spectrum while the methyl was characterised by a singlet at 0.89 ppm.



Scheme 5.7

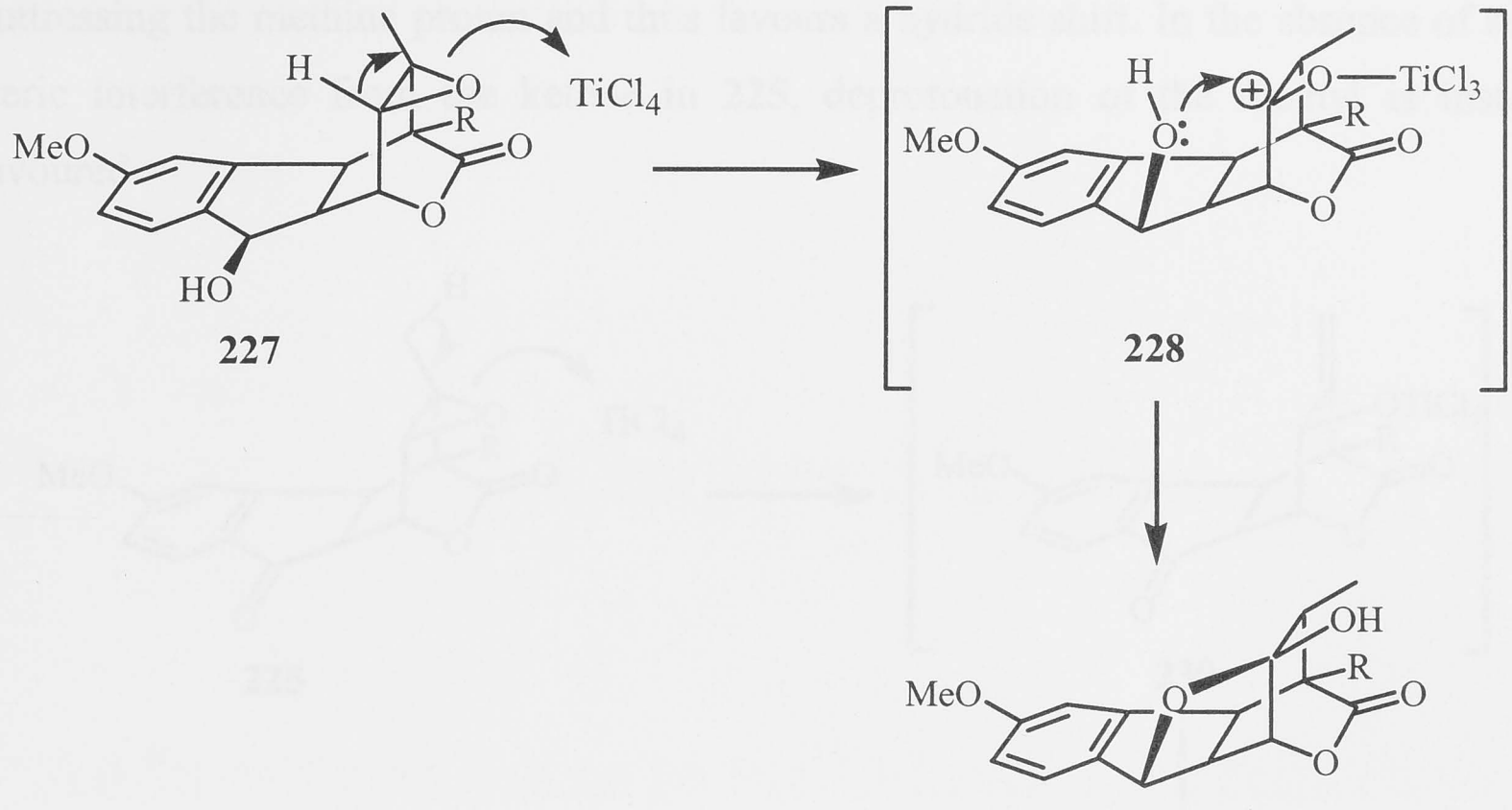
Despite recourse to a wide range of reducing agents, the epoxide function in **225** was wholly resistant to ring-opening. Indeed, the only reaction observed was the occasional reduction of the benzylic ketone.



225 **226**

Scheme 5.8

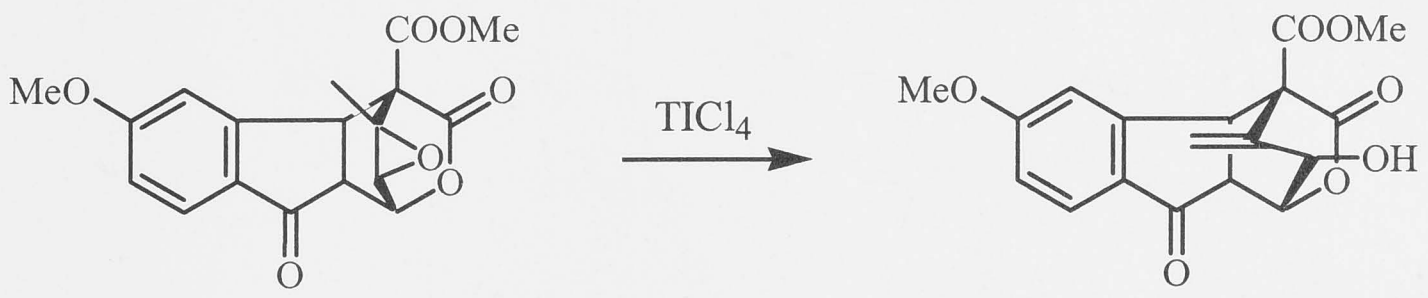
However, when **225** was deliberately reduced to the benzylic alcohol with sodium borohydride in ethanol and treated with a large excess of titanium tetrachloride, an unexpected product was recovered, albeit in a poor 4% yield (Scheme **5.8**). The proton spectrum displayed a doublet (J = 1.16 Hz) at 1.16 ppm, a signal characteristic of a methyl coupled to a methine proton. More importantly, the chemical shift indicated that the methyl was in the *exo* position and no longer under the shielding influence of the aromatic ring – had inversion not occurred, one might expect the methyl to appear at ~0.6 ppm. We initially suspected that the intramolecular hydride shift initiated by complexation of the titanium tetrachloride with the epoxide oxygen was responsible for inversion of the methyl and formation of the diol (Scheme **5.9**). However, the absence of the H-11 proton in the ^{1}H-NMR spectrum and a molecular ion of *m/z* at 346 rather than 348 suggested that the intermediate carbocation **228** was being trapped by the benzylic hydroxyl to form hemi-acetal **226**. This was confirmed by the presence of a peak at 102.25 ppm in the ^{13}C-NMR, a chemical shift which is characteristic of hemi-acetal carbons.



227 **228** **226**

Scheme 5.9

Obviously, the poor yield meant that the above reaction did not constitute a viable alternative to the hydroboration route. We postulated that the benzylic alcohol might be responsible for the poor recovery of product, and so decided to repeat the reaction on the benzylic ketone. Gratifyingly, when titanium tetrachloride was added to a solution of **225**, a single product was obtained in 76% yield (Scheme **5.10**). On initial examination of the ^{1}H-NMR spectrum, however, the methyl peak resonance was no longer visible. Instead, it was replaced by two newly introduced singlets at 5.39 and 5.35 ppm. The chemical shift suggested that these peaks were due to two methylene protons and this conclusion was corroborated by the ^{13}C-NMR spectrum where C10 appeared at 137.74 ppm with the terminal methylene carbon at 121.78 ppm.

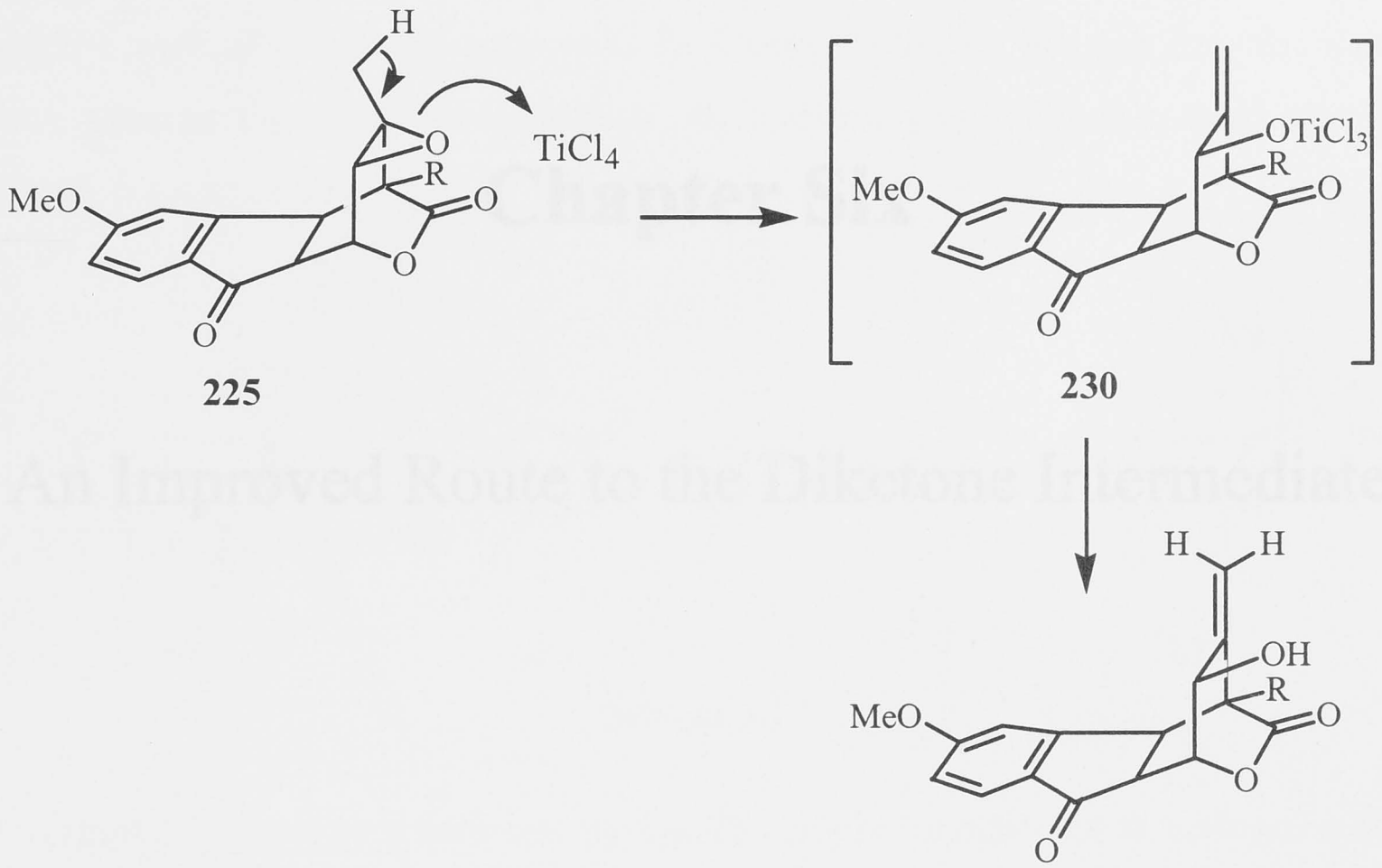


225 **229**

Scheme 5.10

A proposed mechanism for the reaction, outlined in Scheme **5.11**, is based on literature precedent.[104] Once again, the titanium complexes with the oxygen to induce epoxide-opening. However, deprotonation of the methyl group, rather than an intramolecular hydride shift, results in formation of the olefinic bond. As to why this mechanism is favoured is open to argument. One possibility is that the β-hydroxyl in **227** is

buttressing the methine proton and thus favours a hydride shift. In the absence of such steric interference from the ketone in **225**, deprotonation of the methyl is instead favoured.



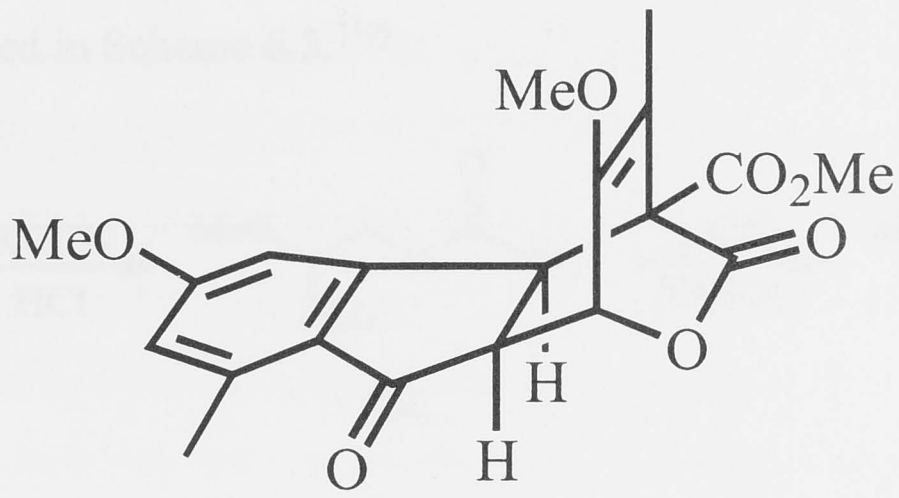
225 **230** **229**

Scheme 5.11

Attempted hydrogenation of **229** with various catalysts was unsuccessful.

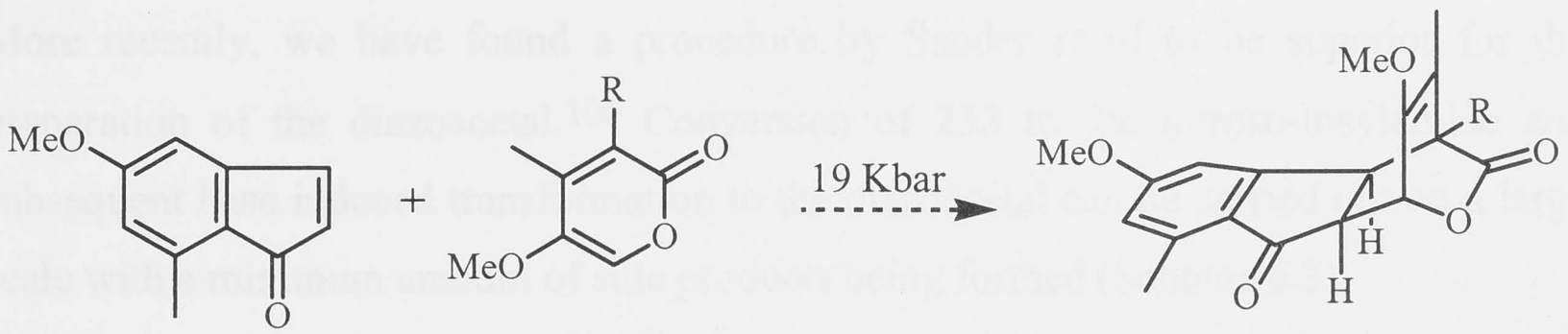
Chapter Six

An Improved Route to the Diketone Intermediate



SECTION 6.1 Preparation of 5-Methoxy Pyrones

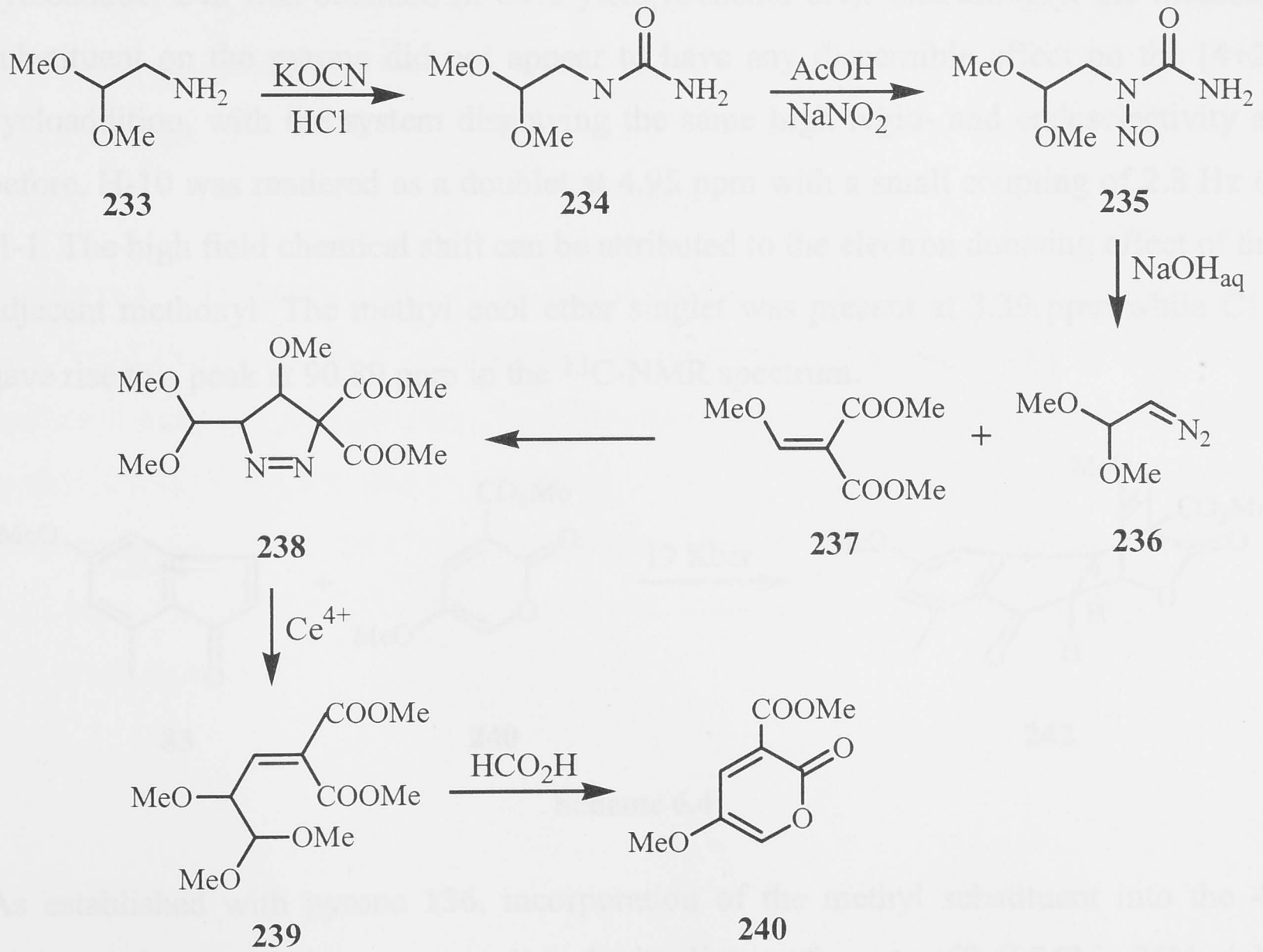
Cogniscent of the difficulties of functionalising the double bond in the cycloadduct, we adopted a radically different approach. By incorporating an oxygen into the starting pyrone prior to the [4+2] cycloaddition, the hydroboration/oxidation steps would be obviated.



83 **231** **232**

Scheme 6.1

For example, 5-methoxy substituted pyrone **231** might be expected to undergo a Diels-Alder reaction to furnish the methyl enol ether (Scheme **6.1**). Subsequent hydrolysis of **232** would then provide the diketone. The previously reported synthesis of 5-methoxy pyrone **240** is outlined in Scheme **6.2**.[105]



233 **234** **235**

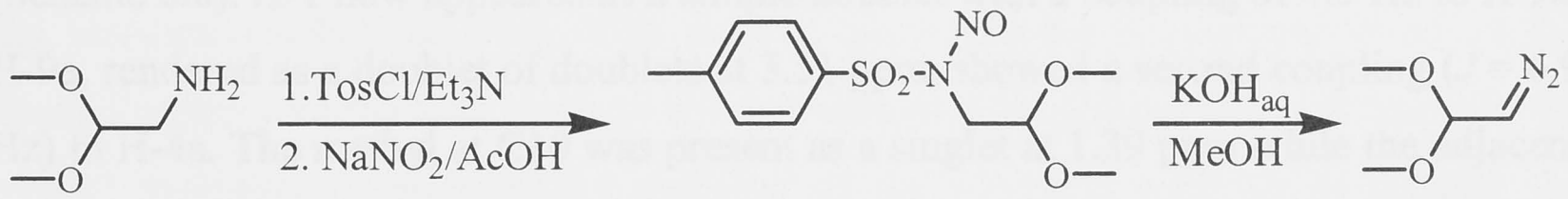
238 **237** **236**

239 **240**

Scheme 6.2

Aminoacetal **233** is converted to the urea **234** which is in turn nitrosated to nitroso-urea **235**. Exposure to aqueous sodium hydroxide generates the reactive diazoacetal **236** which undergoes a cycloaddition reaction with malonate **237** to afford the pyrazoline **238**. Heating **238** in acetone in the presence of 0.2 equivalents of ceric ammonium nitrate results in extrusion of nitrogen and generation of an intermediate diradical species which rearranges to pyrone precursor **239**. Finally, reflux in formic acid furnishes the 5-methoxy substituted pyrone **240**.

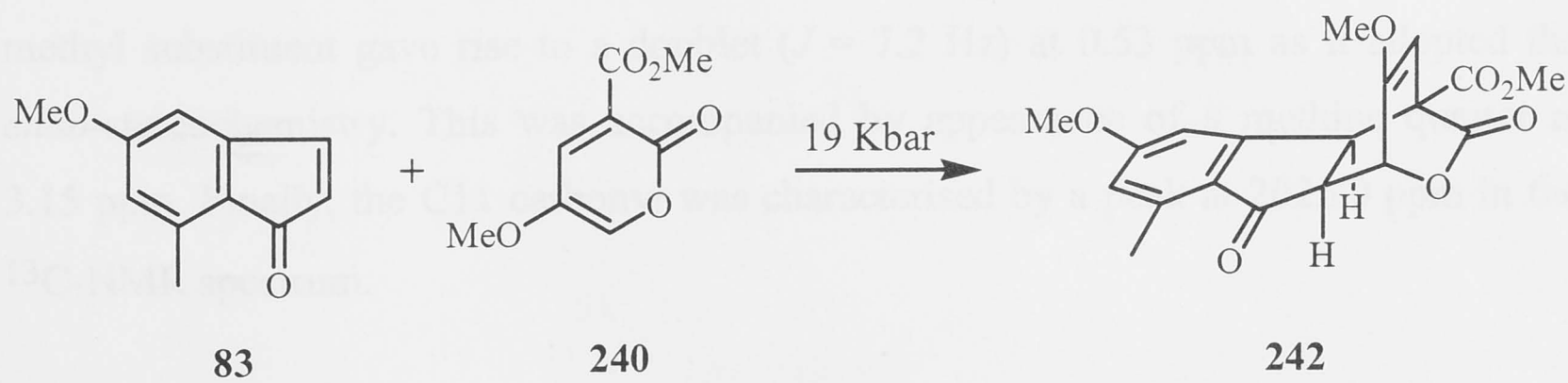
More recently, we have found a procedure by Sander *et al* to be superior for the preparation of the diazoacetal.[106] Conversion of **233** to the nitroso-tosylamide and subsequent base induced transformation to the diazoacetal can be carried out on a large scale with a minimum amount of side products being formed (Scheme **6.3**).



233 **241** **236**

Scheme 6.3

When the new pyrone and indenone **83** were subjected to 19 Kbar for 24 hours, cycloadduct **242** was obtained in 64% yield (Scheme **6.4**). Interestingly, the methoxy substituent on the pyrone did not appear to have any discernible effect on the [4+2] cycloaddition, with the system displaying the same high regio- and endoselectivity as before. H-10 was rendered as a doublet at 4.95 ppm with a small coupling of 2.8 Hz to H-1. The high field chemical shift can be attributed to the electron donating effect of the adjacent methoxyl. The methyl enol ether singlet was present at 3.39 ppm while C10 gave rise to a peak at 90.89 ppm in the ^{13}C-NMR spectrum.

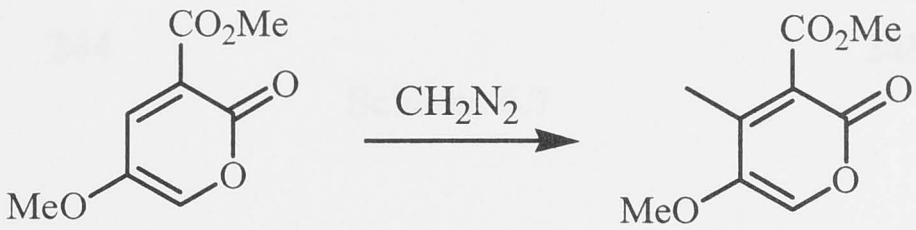


83 **240** **242**

Scheme 6.4

As established with pyrone **136**, incorporation of the methyl substituent into the 4-position of pyrone **240** was accomplished with diazomethane to afford **243** in 75% yield

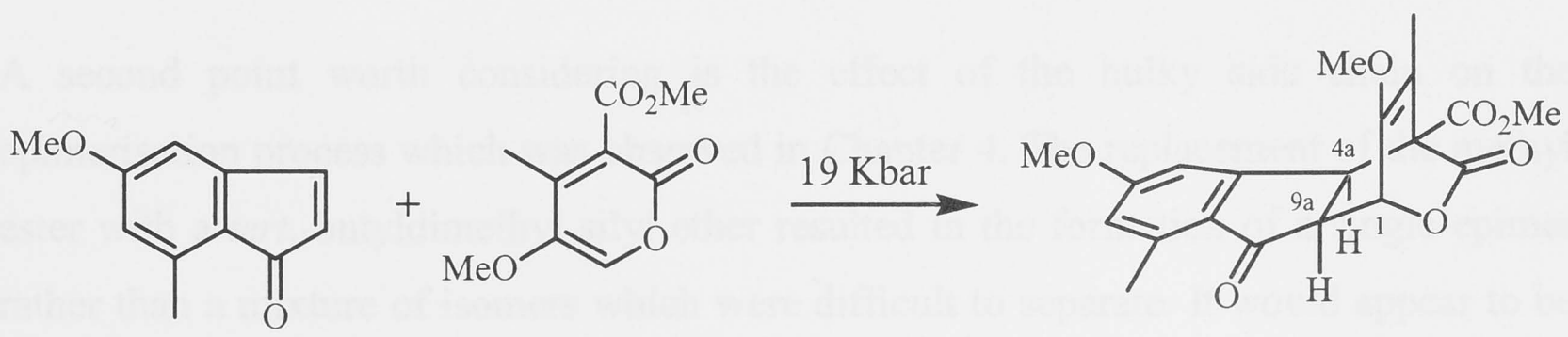
(Scheme **6.5**). The ^{1}H-NMR spectrum was characterised by the downfield singlet of H-6 at 7.07 ppm and the methyl singlet at 2.17 ppm. Introduction of the methyl was confirmed by a molecular ion at *m/z* 172 in the mass spectrum.



240 **243**

Scheme 6.5

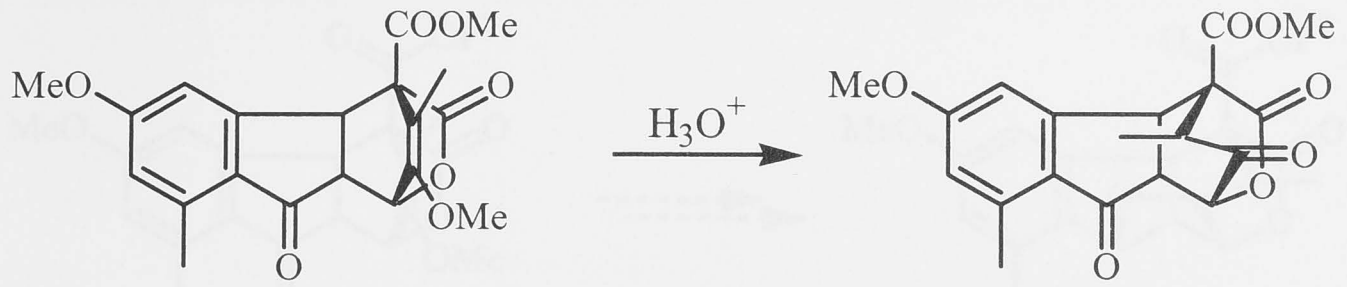
A mixture of the newly formed pyrone **243** and indenone **83** were subjected to high pressure for 24 hours, at which point cycloadduct **244** was obtained in 65% yield (Scheme **6.6**). H-1 now appeared as a simple doublet with a coupling of 4.5 Hz to H-9a. H-9a, rendered as a doublet of doublets at 3.51 ppm, showed a second coupling (J = 6.9 Hz) to H-4a. The methyl at C10 was present as a singlet at 1.39 ppm while the adjacent methoxyl appeared at 3.57 ppm.



83 **243** **244**

Scheme 6.6

Hydrolysis of the methyl enol ether with trifluoroacetic acid afforded diketone **245** in 73% yield (Scheme **6.7**). Conversion to the diketone was accompanied by loss of the methoxyl peak at 3.57 ppm from the NMR spectrum of **245**. More tellingly, the bridge methyl substituent gave rise to a doublet (J = 7.2 Hz) at 0.53 ppm as it adopted the *endo*-stereochemistry. This was accompanied by appearance of a methine quartet at 3.15 ppm. Finally, the C11 carbonyl was characterised by a peak at 202.90 ppm in the ^{13}C-NMR spectrum.



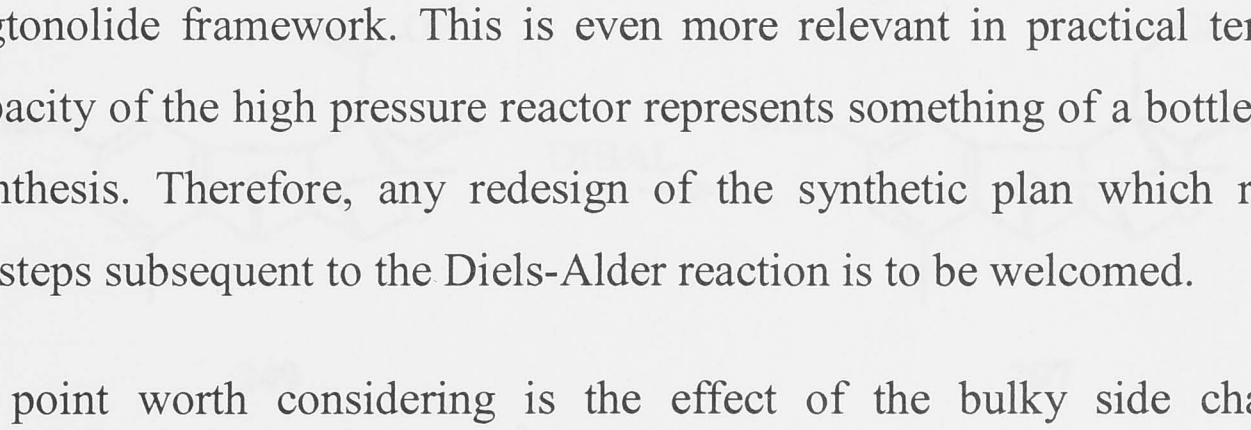
244 **245**

Scheme 6.7

SECTION 6.2 Future Directions

Clearly, the development of the 5-methoxy pyrone chemistry outlined above marks a considerable improvement in both the convergence and efficiency of the construction of the harringtonolide framework. This is even more relevant in practical terms, as the limited capacity of the high pressure reactor represents something of a bottleneck in the overall synthesis. Therefore, any redesign of the synthetic plan which reduces the number of steps subsequent to the Diels-Alder reaction is to be welcomed.

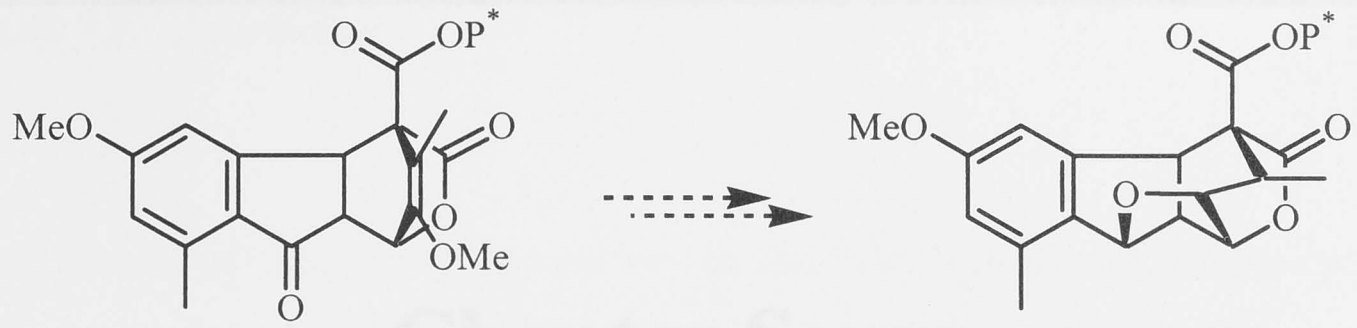
A second point worth considering is the effect of the bulky side chain on the epimerisation process which was observed in Chapter 4. The replacement of the methyl ester with a *tert.*-butyldimethyl silyl ether resulted in the formation of a single epimer rather than a mixture of isomers which were difficult to separate. It would appear to be beneficial, therefore, to incorporate a similarly bulky group into the parent pyrone. Ideally, this would take the form of a chiral auxiliary such as those used by Posner *et al.* in their work directed towards 1α-hydroxyvitamin D_3 steroids (Scheme **6.8**).[107] This should, of course, also provide us with an enantioselective synthesis of harringtonolide.



246 **247**

Scheme 6.8

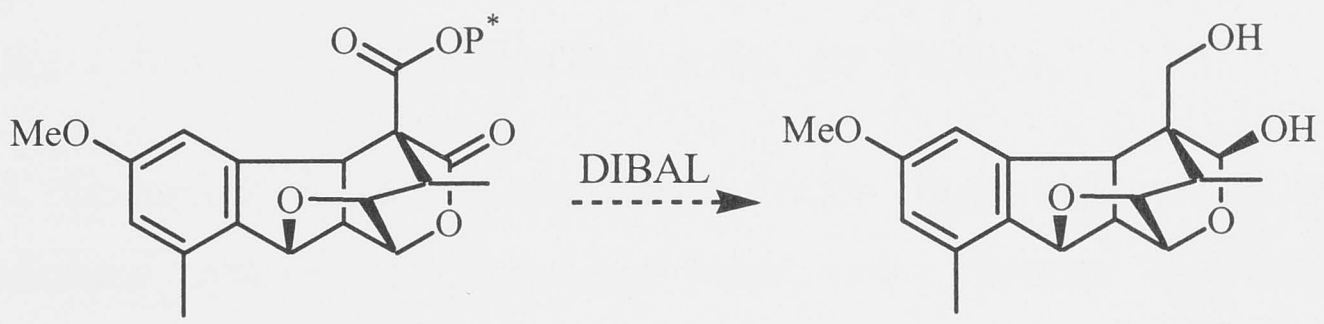
The exact choice of the auxiliary should also take into consideration subsequent reaction conditions *i.e.* it should be stable to the acidic hydrolysis of the methyl enol ether and to the installation of the tetrahydrofuran moiety (Scheme **6.9**).



248 **249**

Scheme 6.9

As it will be necessary to mask the lactone as the silyl ether derivative, it may be possible to eliminate some steps by reducing the lactone and carboxy ester simultaneously (Scheme **6.10**). We have already demonstrated in Chapter 4 that it is possible to differentiate between the two hydroxyls in racemic **207** and to preferentially protect the primary alcohol over the hemi-acetal.



249 **207**

Scheme 6.10

Chapter Seven

Conclusion

SECTION 7.1 Conclusion

We have discovered that the alkene moiety in the first 2-pyrone/indenone cycloadduct that was prepared was unexpectedly unreactive, and severely limited the number of possible approaches leading to harringtonolide. By incorporating a methyl group into the pyrone, however, we have established methodology for manipulation of the bridge stereochemistry, installation of the internal ether bond and homologation of the carboxy ester through to an advanced α-diazoketone intermediate.

Unfortunately, intramolecular arene cyclopropanation was not observed, most likely due to ylide formation with the lactone functionality. However, the protection of the lactone as a hemi-acetal silyl ether is outlined in Chapter 4 and we are optimistic that this modification will successfully prevent undesirable side reactions.

A sound theoretical basis for the unexpectedly high regioselectivity of the pyrone/indenone system has been established using frontier molecular orbital calculations.

Finally, we have described in Chapter 6 a highly convergent route which incorporates oxygen into the parent pyrone and provides more direct and efficient access to the advanced diketone intermediate.

Chapter Eight

Experimental

GENERAL DIRECTIONS

Melting points (mp) were recorded on a Reichert hot-stage and are uncorrected. Microanalyses were conducted by the Australian National University Analytical Services Unit, Canberra.

Low resolution EI mass (LRMS) spectra (70 eV) and high resolution accurate mass measurements (HRMS) were recorded on a VG Autospec double focussing mass spectrometer. The molecular ion (M^+), if present, significant high mass ions and the more intense low mass ions are reported. Data are presented in the following order: *m/z* value; relative intensity as a percentage of the base peak.

Infrared (IR) spectra (ν_{max}) were recorded on a Perkin-Elmer 683 Infrared spectrophotometer in 0.25 mm NaCl solution cells or recorded on a Perkin-Elmer 1800 Fourier Transform Infrared spectrophotometer in KBr plates. Data are recorded as follows: wavenumber (cm^{-1}), intensity (**w**: weak, **m**: medium, **s**: strong).

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) were recorded on Varian Gemini 300 spectrometer at 75.5 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. For proton spectra recorded in deuterated chloroform, the residual peak of $CHCl_3$ was used as the internal reference (7.25 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. Data are recorded as follows: chemical shift, numbers of protons, multiplicity (**s**: singlet, **d**: doublet, **t**: triplet, **q**: quartet, **m**: multiplet, **dd**: doublet of doublets, **ddd**: double doublet of doublets, **br s**: broad singlet), coupling constant (Hz), and assignment (based on chemical shift and homodecoupling experiments).

Two dimensional NMR experiments were recorded on the following instruments: Varian Gemini 300 and Varian Inova 500 spectrometers. The pulse sequences used were homonuclear (^{1}H/^{1}H) correlation spectroscopy (**COSY**), heteronuclear (^{1}H/^{13}C) correlation spectroscopy (**HETCOR**) and ^{1}H-^{13}C correlation via long-range couplings (**HMBC**).[96]

Analytical thin layer chromatography (TLC) was carried out on Merck aluminum TLC plates precoated with silica KG60 F_{254}. The developed plates were visualised under shortwave ultraviolet light and stained with a solution of vanillin (0.5 g) and concentrated sulfuric acid (5 ml) in acetic acid (15 ml) and ethanol (85 ml) at 180°C. Flash chromatography was conducted according to the method of Still and coworkers,[108] with Merck Kieselgel 60 silica gel being used as the adsorbent unless indicated otherwise. All solvents used for elution were analytical reagent (AR) grade obtained from the Ajax Chemical Company and were used without further purification.

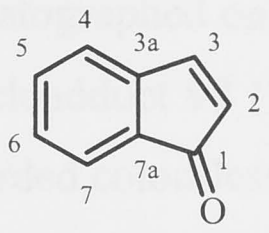
Starting materials and reagents used in reactions were obtained commercially from either the Merck, Aldrich, Fluka or Ajax Chemical Companies and were used without purification, unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (ether), toluene and benzene were purified by distillation from sodium benzophenone-ketyl. Methanol, triethylamine, dichloromethane and 1,2-dichloroethane were purified by distillation from calcium hydride. Ethanol-free ethereal diazomethane[109] was prepared from Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide), which, with rhodium (II) acetate [$Rh_2(OAc)_4$], palladium acetate [$Pd(OAc)_2$] and palladium on carbon (Pd/C, 10%) were purchased from the Aldrich Chemical Company; all reagents were used as supplied. The following catalysts were prepared by literature procedures: (*N*-*t*.-butylsalicylaldiminato)$_2$ copper (II)[110] and copper (II) acetylacetonate [$Cu(acac)_2$].[111]

All moisture-sensitive reactions were conducted in flame-dried glassware under a positive pressure of dry nitrogen; reagents and starting materials were accordingly transferred via syringe or cannula as indicated. Unless otherwise stated, other reactions were also performed under a dry nitrogen atmosphere. Reaction temperatures refer to the external oil bath temperature. All organic extracts were dried with anhydrous magnesium sulfate. After filtration, the bulk of the solvent was removed on a Büchi rotatory evaporator. The last traces of solvent were removed under high vacuum.

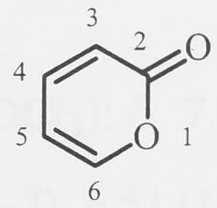
High pressure cycloaddition reactions were carried out in a Psika High Pressure Reactor.

NOTES ON NOMENCLATURE

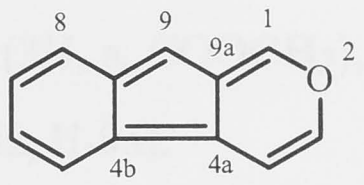
The nomenclature system used in this dissertation conforms to the indexing policies of the Chemical Abstracts Service (CA Index Guide) which are generally in accordance with the rules published by the International Union of Pure and Applied Chemistry (IUPAC). The base structures for parts of the compounds named in the experimental sections are presented below.



Indenone

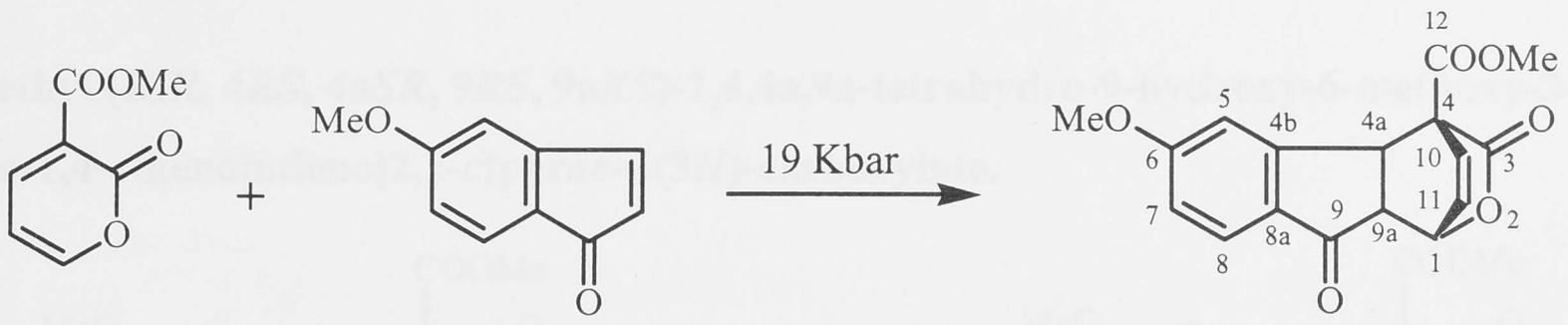


2*H*-Pyran-2-one



Indeno[2,1-*c*]pyran

Methyl (1*SR*, 4*RS* , 4a*SR*, 9a*SR*)-1,4,4a,9a-tetrahydro-6-methoxy-3,9-dioxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



97 **93** **98**

The indenone **93** (550 mg, 3.44 mmol) and the pyrone **97** (504 mg, 3.27 mmol) were dissolved in dichloromethane (1 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the cycloadduct **98** (736 mg, 72%, based on pyrone). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 131-133°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.62 (1H, d, $J_{8,7}$ = 8.6 Hz, H-8), 6.94 (1H, dd, $J_{7,8}$ = 8.6 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.51 (1H, d, $J_{5,7}$ = 2.0 Hz, H-5), 6.36 (2H, m, H-10, H-11), 5.45 (1H, ddd, $J_{1,9a}$ = 5.0 Hz, $J_{1,11}$ = 5.4 Hz, $J_{1,10}$ = 2.0 Hz, H-1), 4.32 (1H, d, $J_{4a,9a}$ = 7.1 Hz, H-4a), 4.03 (3H, s, COO**CH$_3$**), 3.85 (3H, s, **CH$_3$**O-C6), 3.63 (1H, dd, $J_{9a,4a}$ = 7.1 Hz, $J_{9a,1}$ = 5.0 Hz, H-9a).

^{13}C-NMR (75MHz, $CDCl_3$): δ 199.00 (C9), 169.48 (C3), 168.13 (C12), 166.14 (C6), 154.00 (C4b), 132.03 (C8a), 130.57 (C11), 129.75 (C10), 126.24 (C8), 117.05 (C5), 109.87 (C7), 74.95 (C1), 59.90 (C4), 56.09 (**CH$_3$**O-C6), 53.74 (COO**CH$_3$**), 52.83 (C9a), 39.50 (C4a).

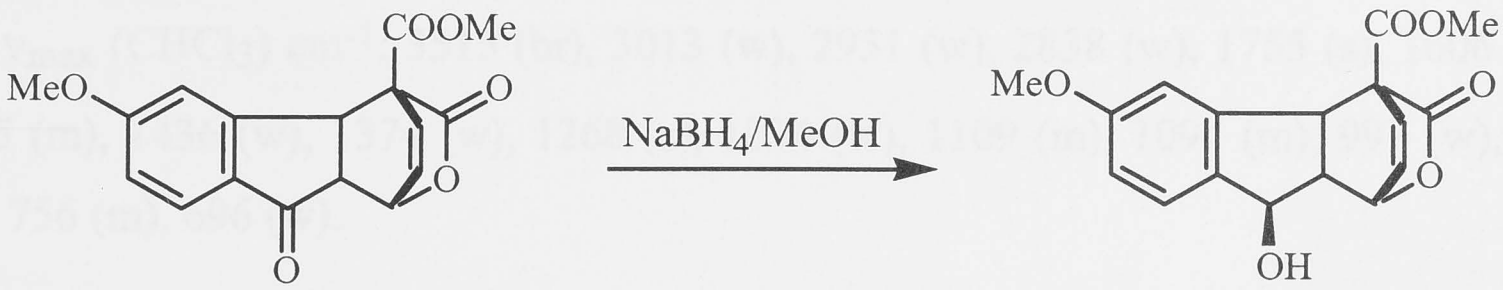
LRMS (*m/z*): 314 (M^+, 24%), 268 (3), 242 (27), 226 (4), 211 (100), 168 (20), 160 (93), 139 (29), 134 (29), 123 (6), 106 (35), 91 (3), 77 (10), 63 (26).

HRMS (EI): Found 314.0787 (M^+), $C_{17}H_{14}O_6$ requires 314.0790.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3085 (w), 3011 (w), 2953 (w), 2842 (w), 1763 (s), 1740 (s), 1705 (s), 1597 (s), 1491 (w), 1458 (w), 1439 (w), 1350 (w), 1308 (m), 1284 (m), 1256 (s), 1196 (w), 1169 (w), 1127 (w), 1109 (w), 1092 (m), 1077 (m), 1069 (m), 1024 (w), 981 (w), 962 (w), 740 (w).

Analysis: Calcd for $C_{17}H_{14}O_6$: C, 64.97%; H, 4.49%. Found: C, 64.51%; H, 4.79%.

Methyl (1*SR*, 4*RS*, 4a*SR*, 9*RS*, 9a*RS*)-1,4,4a,9a-tetrahydro-9-hydroxy-6-methoxy-3-oxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



98 **130**

Sodium borohydride (3 mg, 0.31 mmol) was added to the ketone **98** (50 mg, 0.16 mmol) in a 1:1 solution of dichloromethane/methanol (5 ml) and stirred for 6 hours at room temperature. Acetone (1 ml) was added to decompose the excess borohydride. The solution was acidified with 2M HCl (1 ml) and extracted with ethyl acetate (3x20 ml). The organic phase was washed with brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the alcohol **130** (39 mg, 77%). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 139-141°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.22 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.85 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.51 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.48 (1H, dd, $J_{11,10}$ = 4.5 Hz, $J_{11,1}$ = 4.1 Hz, H-11), 6.38 (1H, dd, $J_{10,11}$ = 4.5 Hz, $J_{10,1}$ = 2.1 Hz, H-10), 5.45 (1H, ddd, $J_{1,9a}$ = 4.0 Hz, $J_{1,11}$ = 4.1 Hz, $J_{1,10}$ = 2.1 Hz, H-1), 5.34 (1H, d, $J_{9,9a}$ = 8.8 Hz, H-9), 4.27 (1H, d, $J_{4a,9a}$ = 8.2 Hz, H-4a), 4.04 (3H, s, COO**CH_3**), 3.75 (3H, s, **CH_3**O-C6), 3.64 (1H, ddd, $J_{9a,4a}$ = 8.2 Hz, $J_{9a,9}$ = 8.8 Hz, $J_{9a,1}$ = 4.0 Hz, H-9a).

^{13}C-NMR (75MHz, $CDCl_3$): δ 171.31 (C3), 169.11 (C12), 161.38 (C6), 140.68 (C4b), 138.16 (C8a), 131.41 (C11), 130.46 (C10), 126.13 (C8), 115.91 (C5), 109.24 (C7), 76.26 (C1), 73.57 (C9), 60.88 (C4), 55.89 (**CH_3**O-C6), 53.75 (COO**CH_3**), 47.04 (C9a), 45.01 (C4a).

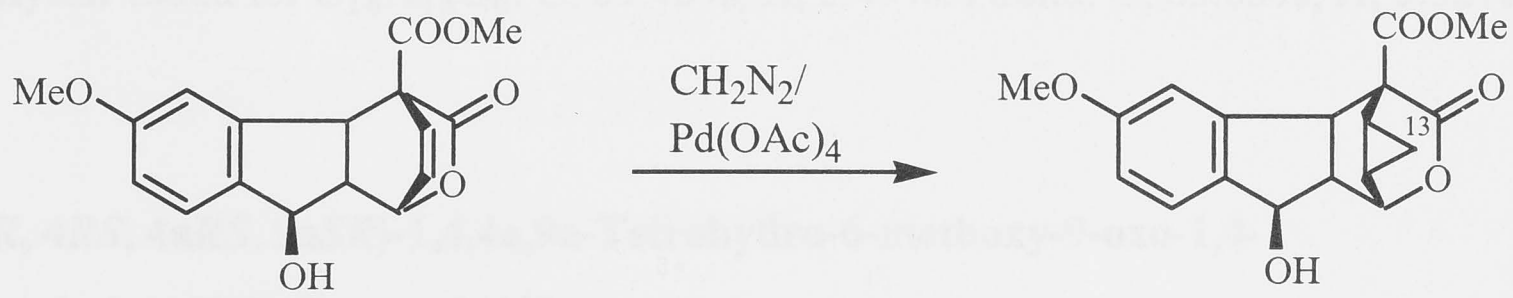
LRMS (*m/z*): 316 (M^+, 28%), 290 (48), 272 (64), 254 (56), 240 (50), 223 (24), 211 (57), 195 (77), 184 (45), 162 (100), 152 (50), 135 (36), 115 (37), 102 (19), 91 (27), 77 (29), 63 (17).

HRMS (EI): Found 316.0945 (M^+), $C_{17}H_{16}O_6$ requires 316.0947.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3515 (br), 3013 (w), 2951 (w), 2838 (w), 1755 (s), 1606 (m), 1495 (m), 1436 (w), 1374 (w), 1268 (s), 1234 (w), 1109 (m), 1094 (m), 997 (w), 842 (w), 756 (m), 696 (w).

Analysis: Calcd for $C_{17}H_{16}O_6$: C, 64.55%; H, 5.10%. Found: C, 64.72%; H, 5.17%.

Methyl (1*SR*, 4*RS*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-1,4,4a,9a-tetrahydro-9-hydroxy-10,11-methano-6-methoxy-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



130 **125**

The alcohol **130** (20 mg, 0.06 mmol) and palladium acetate (1 mg, 0.004 mmol) were dissolved in dichloromethane (5 ml). An excess of ethereal diazomethane (~10 equiv) was added over 30 minutes at 0°C. The solution was stirred at room temperature for 16 hours until the yellow colour had disappeared. The solvent was removed under reduced pressure and the residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the cyclopropyl product **125** (20 mg, 95%). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p.: 129-130°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.28 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.89 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.56 (1H, d, $J_{5,7}$ = 2.4 Hz, H-5), 5.49 (1H, d, $J_{9,9a}$ = 8.9 Hz, H-9), 5.06 (1H, d, $J_{1,9a}$ = 3.3 Hz, H-1), 4.09 (1H, d, $J_{4a,9a}$ = 9.2 Hz, H-4a), 3.97 (3H, s, COO**CH_3**), 3.77 (3H, s, **CH_3**O-C6), 3.34 (1H, ddd, $J_{9a,4a}$ = 9.2 Hz, $J_{9a,9}$ = 8.9 Hz, $J_{9a,1}$ = 3.3 Hz, H-9a), 1.52 (1H, m, $J_{11,13}$ = 8.0 Hz, $J_{11,10}$ = 4.2 Hz, H-11), 1.07 (1H, m, $J_{10,13}$ = 7.9 Hz, $J_{10,11}$ = 4.2 Hz, H-10), 0.57-0.50 (2H, m, 2x H-13).

^{13}C-NMR (75MHz, $CDCl_3$): δ 171.09 (C3), 170.83 (C12), 160.95 (C6), 140.5 (C4b), 138.28 (C8a), 126.08 (C8), 115.44 (C5), 109.92 (C7), 75.13 (C1), 73.92 (C9), 57.18 (C4), 55.97 (**CH_3**O-C6), 53.69 (COO**CH_3**), 47.27 (C9a), 46.03 (C4a), 10.21 (C11), 9.43 (C10), 3.46 (C13).

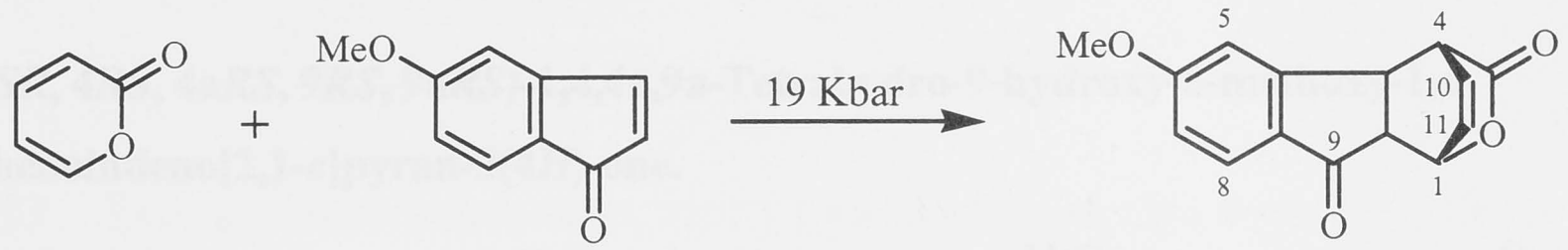
LRMS (*m/z*): 330 (M^+, 87%), 299 (4), 280 (4), 270 (5), 253 (6), 225 (10), 209 (14), 197 (5), 175 (6), 162 (100), 147 (36), 139 (12), 126 (11), 115 (10), 102 (7), 91 (12), 77 (11), 59 (8).

HRMS (EI): Found 330.1102 (M^+), $C_{18}H_{18}O_6$ requires 330.1103.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3530 (br), 3005 (w), 2952 (w), 1754 (s), 1654 (w), 1542 (m), 1496 (w), 1457 (w), 1436 (w), 1375 (w), 1269 (s), 1234 (w), 1109 (m), 1095 (m), 1056 (m), 1033 (w), 997 (w), 873 (w), 741 (w).

Analysis: Calcd for $C_{18}H_{18}O_6$: C, 65.45%; H, 5.49%. Found: C, 65.03%; H, 5.32%.

(1*SR*, 4*RS*, 4a*RS*, 9a*SR*)-1,4,4a,9a-Tetrahydro-6-methoxy-9-oxo-1,4-ethenoindeno[2,1-*c*]pyran-3(4*H*)-one.



133 **93** **134**

The indenone **93** (200 mg, 1.25 mmol) and the pyrone **133** (150 mg, 1.56 mmol) were dissolved in a minimum of dichloromethane (1 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 18 hours. The solvent was removed under reduced pressure and the residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the cycloadduct **134** (137 mg, 43%, based on indenone). Recrystallisation from ethyl acetate afforded colourless needles.

m.p. : 125-126°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.63 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 6.96 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.92 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.34 (1H, ddd, $J_{11,10}$ = 7.9 Hz, $J_{11,1}$ = 5.8 Hz, $J_{11,4}$ = 1.6 Hz, H-11), 6.03 (1H, ddd, $J_{10,11}$ = 7.9 Hz, $J_{10,1}$ = 1.9 Hz,

$J_{10,4}$ = 5.9 Hz, H-10), 5.56 (1H, ddd, $J_{1,9a}$ = 5.0 Hz, $J_{1,11}$ = 5.8 Hz, $J_{1,10}$ = 1.9 Hz, H-1), 3.94 (1H, ddd, $J_{4,4a}$ = 3.6 Hz, $J_{4,10}$ = 5.9 Hz, $J_{4,11}$ = 1.6 Hz, H-4), 3.97 (3H, s, **CH_3**O-C6), 3.82 (1H, dd, $J_{4a,9a}$ = 6.9 Hz, $J_{4a,4}$ = 3.6 Hz, H-4a), 3.34 (1H, dd, $J_{9a,4a}$ = 6.9 Hz, $J_{9a,1}$ = 5.0 Hz, H-9a).

^{13}C-NMR (75MHz, $CDCl_3$): δ 200.35 (C9), 173.12 (C3), 166.59 (C6), 156.08 (C4b), 132.42 (C8a), 130.91 (C11), 130.75 (C10), 126.46 (C8), 117.22 (C5), 109.36 (C7), 75.00 (C1), 56.46 (**CH_3**O-C6), 52.47 (C9a), 46.11 (C4), 37.42 (C4a).

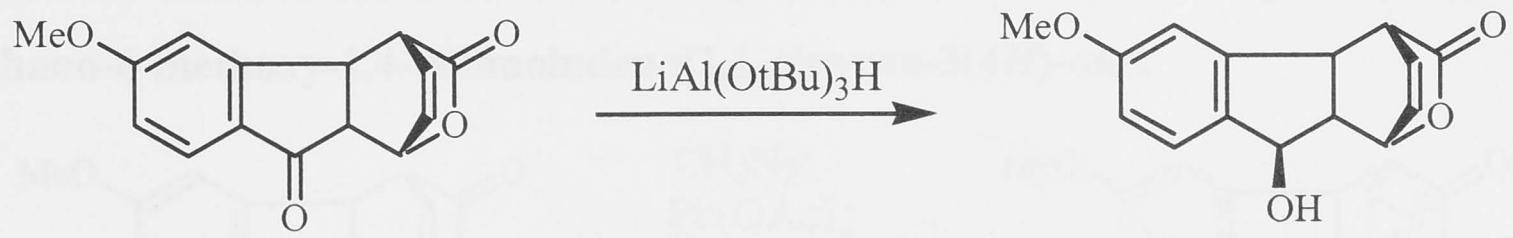
LRMS (*m/z*): 256 (M^+, 45%), 211 (72), 199 (5), 181 (11), 168 (11), 141 (16), 134 (29), 115 (15), 106 (27), 102 (12), 89 (10), 63 (24).

HRMS (EI): Found 256.0738 (M^+), $C_{15}H_{12}O_4$ requires 256.0736.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3013 (w), 2943 (w), 2841 (w), 1757 (s), 1699 (s), 1597 (s), 1490 (w), 1440 (w), 1359 (w), 1345 (m), 1312 (m), 1260 (s), 1176 (m), 1141 (w), 1091 (w), 1007 (m), 971 (m), 813 (w), 738 (w).

Analysis: Calcd for $C_{15}H_{12}O_4$: C, 70.31%; H, 4.72%. Found: C, 70.20%; H, 4.87%.

(1*SR*, 4*RS*, 4a*RS*, 9*RS*, 9a*RS*)-1,4,4a,9a-Tetrahydro-9-hydroxy-6-methoxy-1,4-ethenoindeno[2,1-*c*]pyran-3(4*H*)-one.



134 **249**

The ketone **134** (18 mg, 0.07 mmol) was dissolved in a 4:1 solution of dichloromethane/methanol (2.5 ml). Lithium tri(*tert.*-butoxy)aluminum hydride (28 mg, 0.11 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours under nitrogen. The solution was acidified with 2M HCl (2 ml) and extracted with ethyl acetate (3x10 ml). The organic phase was washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the alcohol **249** (13 mg, 72%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.22 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 6.84 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.68 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.43 (1H, ddd, $J_{11,10}$ = 7.7 Hz, $J_{11,1}$ = 4.9 Hz, $J_{11,4}$ = 1.6 Hz, H-11), 6.04 (1H, ddd, $J_{10,11}$ = 7.7 Hz, $J_{10,1}$ = 1.9 Hz, $J_{10,4}$ = 6.0 Hz, H-10), 5.41 (1H, ddd, $J_{1,9a}$ = 4.3 Hz, $J_{1,11}$ = 4.9 Hz, $J_{1,10}$ = 1.9 Hz, H-1), 5.36 (1H, d, $J_{9,9a}$ = 8.4 Hz, H-9), 3.91 (1H, ddd, $J_{4,4a}$ = 3.4 Hz, $J_{4,11}$ = 1.6 Hz, $J_{4,10}$ = 6.0 Hz, H-4), 3.81 (3H, s, **CH_3**O-C6), 3.76 (1H, dd, $J_{4a,9a}$ = 8.3 Hz, $J_{4a,4}$ = 3.4 Hz, H-4a), 3.55 (1H, ddd, $J_{9a,4a}$ = 8.4 Hz, $J_{9a,1}$ = 4.3 Hz, $J_{9a,9}$ = 8.6 Hz, H-9a).

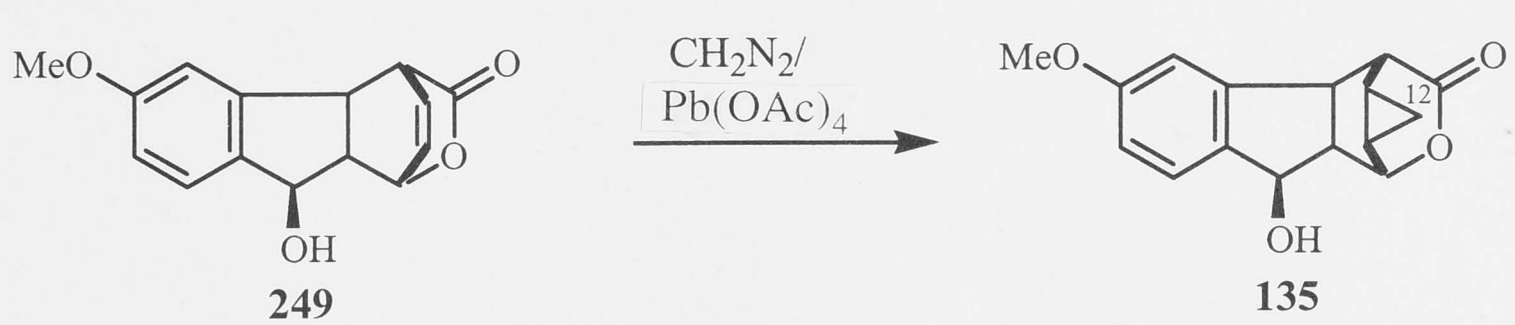
^{13}C-NMR (75MHz, $CDCl_3$): δ 174.38 (C3), 161.53 (C6), 142.48 (C4b), 138.10 (C8a), 131.96 (C11), 130.94 (C10), 126.06 (C8), 115.61 (C5), 108.88 (C7), 75.83 (C1), 74.32 (C9), 56.09 (**CH_3**O-C6), 48.89 (C9a), 46.94 (C4), 44.77 (C4a).

LRMS (*m/z*): 258 (M^+, 43%), 214 (24), 195 (23), 185 (13), 175 (45), 162 (100), 152 (23), 135 (31), 121 (23), 115 (23), 112 (14), 77 (25), 65 (16).

HRMS (EI): Found 258.0891 (M^+), $C_{15}H_{14}O_4$ requires 258.0892.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3435 (br), 3010 (w), 2960 (w), 2925 (w), 2854 (w), 1740 (s), 1608 (m), 1496 (m), 1465 (w), 1368 (w), 1321 (m), 1260 (s), 1181 (w), 1146 (w), 1100 (m), 1069 (m), 1029 (m), 968 (w), 839 (w), 798 (w).

(1*SR*, 4*RS*, 4a*RS*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-1,4,4a,9a-Tetrahydro-9-hydroxy-10,11-methano-6-methoxy-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



249 **135**

The alcohol **249** (30 mg, 0.12 mmol) and palladium acetate (4 mg, 0.018 mmol) were dissolved in dichloromethane (8 ml). An excess of ethereal diazomethane (~10 equiv) was added over 30 minutes at 0°C. The solution was stirred at room temperature for 16 hours until the yellow colour had disappeared. The solvent was removed under reduced pressure and the residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the cyclopropyl product **135** (29 mg, 93%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.28 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 6.90 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.76 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 5.54 (1H, d, $J_{9,9a}$ = 9.3 Hz, H-9), 5.03 (1H, dd, $J_{1,9a}$ = 3.7 Hz, $J_{1,11}$ = 3.3 Hz, H-1), 3.83 (3H, s, **CH_3**O-C6), 3.58 (1H, dd, $J_{4a,9a}$ = 8.9 Hz, $J_{4a,4}$ = 4.0 Hz, H-4a), 3.44 (1H, dd, $J_{4,4a}$ = 4.0 Hz, $J_{4,10}$ = 3.2 Hz, H-4), 3.24 (1H, ddd, $J_{9a,4a}$ = 8.9 Hz, $J_{9a,1}$ = 3.7 Hz, $J_{9a,9}$ = 9.3 Hz, H-9a), 1.40 (1H, m, $J_{11,13}$ = 8.0 Hz, $J_{11,10}$ = 3.3 Hz, $J_{11,1}$ = 3.3 Hz, H-11), 0.83 (1H, m, $J_{10,13}$ = 7.8 Hz, $J_{10,11}$ = 3.2 Hz, H-10), 0.46-0.35 (2H, m, 2x H-12).

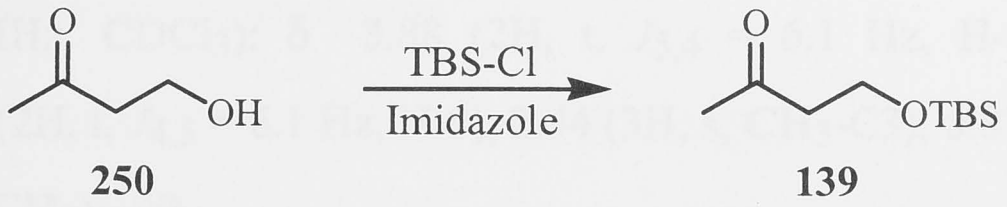
^{13}C-NMR (75MHz, $CDCl_3$): δ 174.18 (C3), 161.15 (C6), 142.24 (C4b), 138.19 (C8a), 125.88 (C8), 115.25 (C5), 109.57 (C7), 74.73 (C1), 74.73 (C9), 56.12 (**CH_3**O-C6), 46.09 (C9a), 43.78 (C4a), 42.45 (C4), 10.14 (C11), 6.48 (C10), 3.00 (C12).

LRMS (*m/z*): 272 (M^+, 93%), 254 (25), 241 (10), 209 (9), 197 (12), 187 (15), 175 (25), 162 (100), 147 (61), 131 (21), 115 (20), 102 (11), 91 (17), 81 (22), 77 (16).

HRMS (EI): Found 272.1048 (M^+), $C_{16}H_{16}O_4$ requires 272.1049.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3459 (br), 3009 (w), 2931 (w), 1754 (s), 1607 (m), 1494 (m), 1465 (w), 1367 (w), 1315 (m), 1265 (m), 1193 (w), 1147 (w), 1110 (w), 1071 (w), 1038 (w), 980 (w), 838 (w), 734 (w).

4-(*tert.*-Butyldimethylsilyloxy)-butan-2-one.



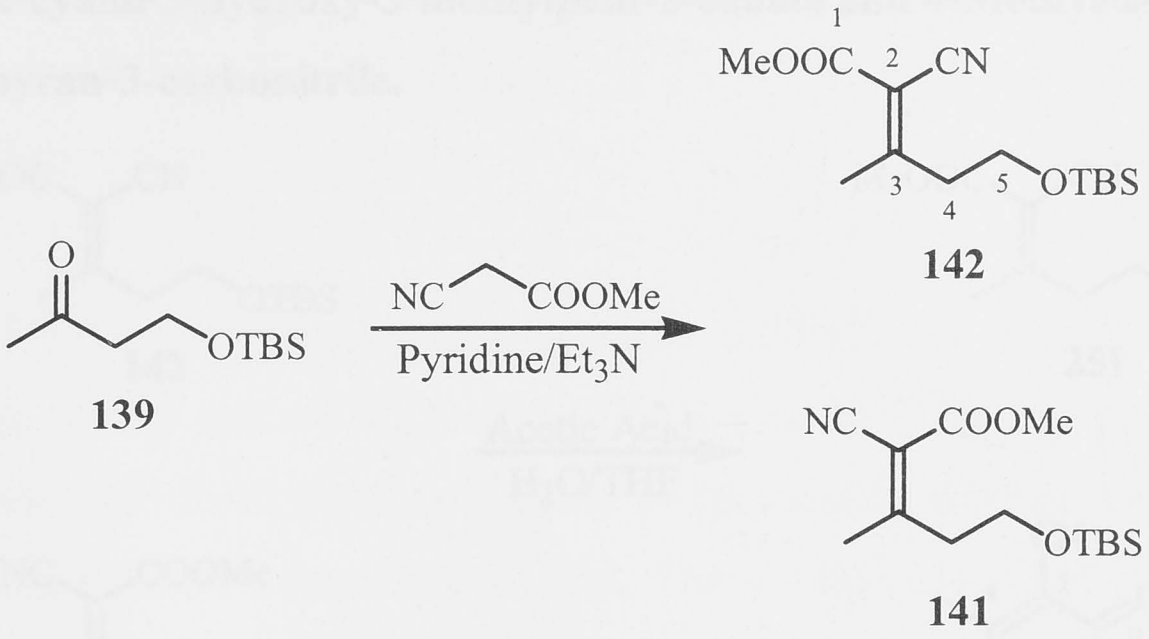
250 **139**

tert.-Butyldimethylsilyl chloride (3.9 g, 0.026 mol) was added to the alcohol **250** (2.0 g, 0.023 mol) and imidazole (2.4 g, 0.035 mol) in dichloromethane (50 ml) and stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 10:1) to yield the product **139** (4.5 g, 98%) as a colourless oil .

^{1}H-NMR (300MHz, $CDCl_3$): δ 3.86 (2H, t, $J_{4,3}$ = 6.2 Hz, H-4), 2.59 (2H, t, $J_{3,4}$ = 6.2 Hz, H-3), 2.15 (3H, s, H-1), 0.85 (9H, s, **$(CH_3)_3$**-C), 0.02 (6H, s, **$(CH_3)_2$**-Si).

^{13}C-NMR (75MHz, $CDCl_3$): δ 208.60 (C2), 59.37 (C4), 47.04 (C3), 31.35 (C1), 26.37 (**$(CH_3)_3$**-C), 18.74 ($(CH_3)_3$-**C**), -4.94 **$(CH_3)_2$**-Si).

Methyl (2*E*)-5-(*tert.*-Butyldimethylsilyloxy)-2-cyano-3-methylpent-2-enoate and Methyl (2*Z*)-5-(*tert.*-Butyldimethylsilyloxy)-2-cyano-3-methylpent-2-enoate.



139 **142**

141

The ketone **139** (1 g, 4.95 mmol) was added to methyl cyanoacetate (490 mg, 4.95 mmol), pyridine (0.5 ml, 4.23 mmol) and triethylamine (0.5 ml, 3.6 mmol) in dichloromethane (10 ml) and stirred at room temperature for 16 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 10:1) to yield an inseparable mixture of isomers **141** and **142** (798 mg, 57%) as a colourless oil.

Methyl (2*E*)-5-(*tert.*-Butyldimethylsilyloxy)-2-cyano-3-methylpent-2-enoate.

^{1}H-NMR (300MHz, $CDCl_3$): δ 3.88 (2H, t, $J_{5,4}$ = 6.1 Hz, H-5), 3.81 (3H, s, COO**CH_3**), 2.79 (2H, t, $J_{4,5}$ = 6.1 Hz, H-4), 2.44 (3H, s, **CH_3**-C3), 0.87 (9H, s, **$(CH_3)_3$**-C), 0.05 (6H, s, **$(CH_3)_2$**-Si).

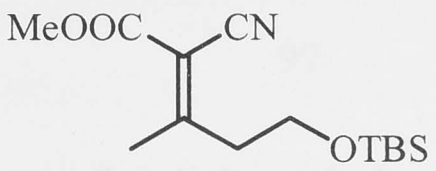
^{13}C-NMR (75MHz, $CDCl_3$): δ 176.52 (C1), 162.91 (C3), 116.15 (**C**N), 106.13 (C2), 61.40 (C5), 53.02 (COO**CH_3**), 44.10 (C4), 27.42 (**CH_3**-C3), 26.35 (**$(CH_3)_3$**-C), 18.73 ($(CH_3)_3$-**C**), -4.98 **$(CH_3)_2$**-Si).

Methyl (2*Z*)-5-(*tert.*-Butyldimethylsilyloxy)-2-cyano-3-methylpent-2-enoate.

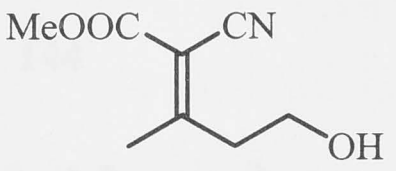
^{1}H-NMR (300MHz, $CDCl_3$): δ 3.84 (2H, t, $J_{5,4}$ = 6.0 Hz, H-5), 3.82 (3H, s, COO**CH_3**), 3.04 (2H, t, $J_{4,5}$ = 6.0 Hz, H-4), 2.37 (3H, s, **CH_3**-C3), 0.87 (9H, s, **$(CH_3)_3$**-C), 0.03 (6H, s, **$(CH_3)_2$**-Si).

^{13}C-NMR (75MHz, $CDCl_3$): δ 177.37 (C1), 162.61 (C3), 116.28 (**C**N), 105.73 (C2), 62.37 (C5), 53.01 (COO**CH_3**), 39.12 (C4), 26.35 (**$(CH_3)_3$**-C), 22.52 (**CH_3**-C3), 18.73 ($(CH_3)_3$-**C**), -4.98 **$(CH_3)_2$**-Si).

Methyl (2*E*)-2-cyano-5-hydroxy-3-methylpent-2-enoate and 4-Methyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile.

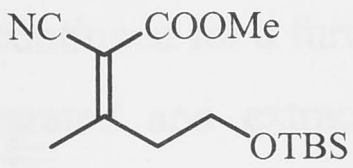


142

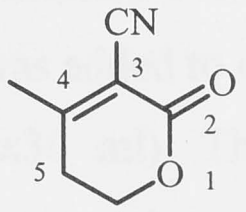


251

Acetic Acid
H_2O/THF



141



143

The mixture of silyl ethers **141** and **142** (500 mg, 1.77 mmol) in acetic acid (3 ml), water (1 ml) and tetrahydrofuran (1 ml) were heated at 50°C for 16 hours. The solution was diluted with ethyl acetate (50 ml), washed with brine (2x5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl

acetate = 2:1) to yield the alcohol **251** (99 mg, 33%) followed by the more polar lactone **143** (63 mg, 26%) both as colourless oils.

Methyl (2*E*)-2-cyano-5-hydroxy-3-methylpent-2-enoate.

^{1}H-NMR (300MHz, $CDCl_3$): δ 3.84 (2H, t, $J_{5,4}$ = 6.4 Hz, H-5), 3.78 (3H, s, COO**CH$_3$**), 2.78 (2H, t, $J_{4,5}$ = 6.4 Hz, H-4), 2.40 (3H, s, **CH$_3$**-C3).

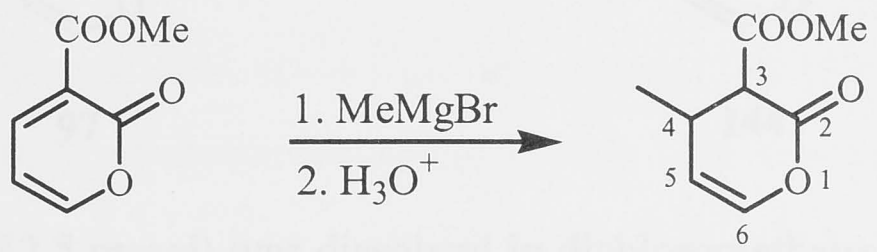
^{13}C-NMR (75MHz, $CDCl_3$): δ 175.99 (C1), 162.77 (C3), 116.35 (**C**N), 106.35 (C2), 60.51 (C5), 53.14 (COO**CH$_3$**), 44.21 (C4), 21.99 (**CH$_3$**-C3).

4-Methyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile.

^{1}H-NMR (300MHz, $CDCl_3$): δ 4.40 (2H, t, $J_{6,5}$ = 6.2 Hz, H-6), 2.65 (2H, t, $J_{5,6}$ = 6.1 Hz, H-5), 2.39 (3H, s, **CH$_3$**-C4).

^{13}C-NMR (75MHz, $CDCl_3$): δ 174.72 (C2), 162.57 (C4), 115.94 (**C**N), 104.85 (C3), 60.61 (C6), 52.73 (C5), 27.60 (**CH$_3$**-C4).

Methyl 4-methyl-2-oxo-3,4-dihydro-2*H*-pyran-3-carboxylate.



97 **144**

A solution of 1.4M methylmagnesium bromide (850 µl, 1.2 mmol) was added to tetrahydrofuran (2 ml) and cooled to 0°C. The pyrone **97** (100 mg, 0.65 mmol) was dissolved in tetrahydrofuran (2 ml) and added to the reaction mixture over 10 minutes. Stirring was continued for a further 30 minutes. The solution was added to cold 1M HCl (10 ml), separated and extracted with dichloromethane (3x30 ml). The combined organic phase was washed with brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the product **144** (60 mg, 54%) as a white paste.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.47 (1H, d, $J_{6,5}$ = 5.9 Hz, $J_{6,4}$ = 1.8 Hz, H-6), 5.24 (1H, dd, $J_{5,6}$ = 5.9 Hz, $J_{5,4}$ = 3.6 Hz, H-5), 3.80 (3H, s, COO**CH$_3$**), 3.33 (1H, d, $J_{3,4}$ =

8.9 Hz, H-3), 3.06 (1H, dddq, $J_{4,3}$ = 8.9 Hz, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 3.6 Hz, $J_{4,Me}$ = 7.0 Hz, H-4), 1.14 (3H, d, $J_{Me,4}$ = 7.0 Hz, **CH_3**-C4).

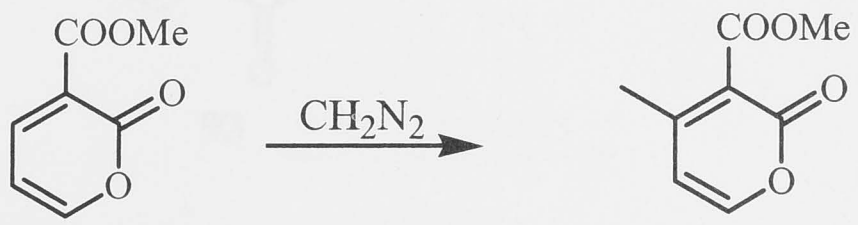
^{13}C-NMR (75MHz, $CDCl_3$): δ 168.77 (**C**$OOCH_3$), 165.26 (C2), 140.63 (C6), 111.60 (C5), 53.96 (C3), 53.49 (COO**CH_3**), 29.75 (C4), 19.67 (**CH_3**-C4).

LRMS (*m/z*): 171 (M^+ + H, 100%), 155 (16), 139 (17), 123 (33), 111 (100), 101 (37), 82 (26), 69 (87), 59 (25).

HRMS (EI): Found 171.0659 (M^+ + H), $C_8H_{11}O_4$ requires 171.0657.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3012 (w), 2966 (w), 2929 (w), 2883 (w), 1751 (s), 1734 (s), 1658 (m), 1452 (w), 1433 (w), 1389 (w), 1355 (w), 1323 (w), 1294 (w), 1261 (w), 1228 (m), 1192 (m), 1159 (m), 1089 (w), 1040 (s), 941 (w), 812 (w), 757 (m).

Methyl 4-methyl-2-oxo-2*H*-pyran-3-carboxylate.



97 **144**

The pyrone **97** (5 g, 32.5 mmol) was dissolved in dichloromethane (100 ml) and cooled to 0°C. Ethereal diazomethane was added in portions over 1 hour until all the starting material had been consumed. Stirring at room temperature was continued for a further 16 hours. The solvent was removed under reduced pressure and the residue was chromatographed directly on silica gel (petroleum ether : ethyl acetate = 1:1) to yield the pyrone **144** (4.525 g, 82%). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 86-88°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.44 (1H, d, $J_{6,5}$ = 5.4 Hz, H-6), 6.14 (1H, d, $J_{5,6}$ = 5.4 Hz, H-5), 3.91 (3H, s, COO**CH_3**), 2.26 (3H, s, **CH_3**-C4).

^{13}C-NMR (75MHz, $CDCl_3$): δ 165.49 (**C**$OOCH_3$), 159.51 (C2), 156.02 (C4), 151.85 (C6), 119.89 (C3), 110.33 (C5), 53.25 (COO**CH_3**), 20.74 (**CH_3**-C4).

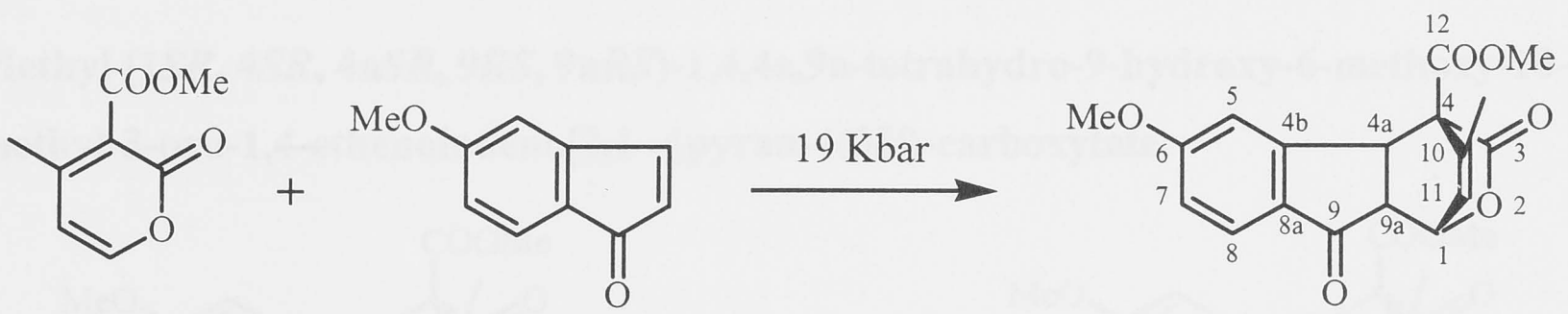
LRMS (*m/z*): 168 (M^+, 73%), 140 (89), 137 (100), 125 (13), 112 (72), 109 (92), 97 (33), 82 (45), 67 (31), 59 (17).

HRMS (EI): Found 168.0421 (M^+), $C_8H_8O_4$ requires 168.0423.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3070 (w), 2970 (w), 1740 (m), 1701 (s), 1633 (m), 1546 (s), 1423 (m), 1318 (m), 1268 (m), 1254 (m), 1185 (w), 1144 (w), 1094 (m), 1033 (m), 832 (m), 814 (m), 790 (m).

Analysis: Calcd for $C_8H_8O_4$: C, 57.14%; H, 4.80%. Found: C, 56.88%; H, 4.73%.

Methyl (1*SR*, 4*SR*, 4a*SR*, 9a*SR*)-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-3,9-dioxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



136 **93** **137**

The indenone **93** (500 mg, 1.05 mmol) and the pyrone **136** (500 mg, 1 mmol) were dissolved in a minimum of dichloromethane (1 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 20 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the cycloadduct **137** (713 mg, 73%, based on pyrone). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p.: 129-131°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.63 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 7.12 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.95 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 5.97 (1H, d, $J_{11,1}$ = 5.0 Hz, H-11), 5.56 (1H, dd, $J_{1,9a}$ = 4.9 Hz, $J_{1,11}$ = 5.0 Hz, H-1), 4.39 (1H, d, $J_{4a,9a}$ = 6.8 Hz, H-4a), 4.03 (3H, s, COO**CH_3**), 3.86 (3H, s, **CH_3**O-C6), 3.53 (1H, dd, $J_{9a,4a}$ = 6.8 Hz, $J_{9a,1}$ = 4.9 Hz, H-9a), 1.55 (3H, s, **CH_3**-C10).

^{13}C-NMR (75MHz, $CDCl_3$): δ 200.35 (C9), 170.55 (C3), 168.75 (C12), 166.29 (C6), 154.69 (C4b), 140.59 (C10), 132.64 (C8a), 126.54 (C8), 124.29 (C11), 117.11 (C5),

111.26 (C7), 74.54 (C1), 63.78 (C4), 56.40 (**CH_3**O-C6), 53.69 (COO**CH_3**), 53.34 (C9a), 39.80 (C4a), 20.44 (**CH_3**-C10).

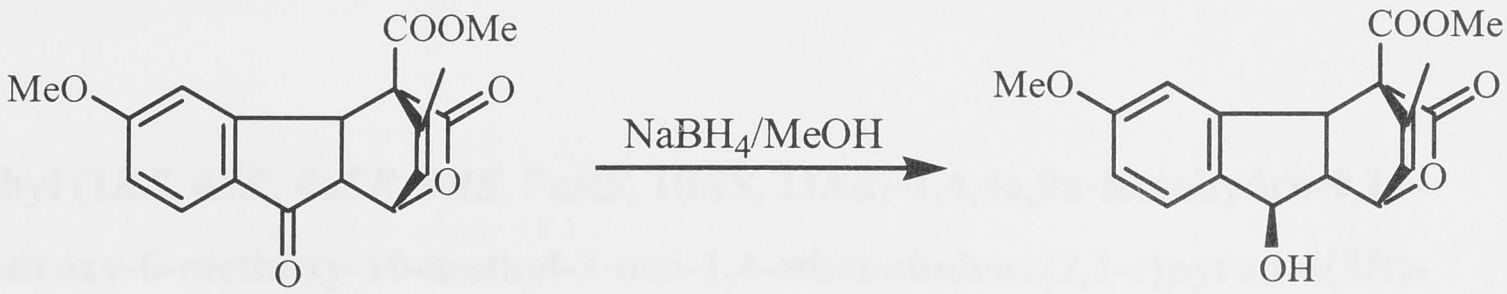
LRMS (*m/z*): 328 (M^+, 29%), 282 (3), 253 (4), 225 (89), 210 (4), 184 (10), 160 (100), 153 (12), 134 (14), 106 (17), 63 (14).

HRMS (EI): Found 328.0944 (M^+), $C_{18}H_{16}O_6$ requires 328.0947.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3000 (w), 2953 (w), 2906 (w), 1745 (s), 1692 (s), 1591 (s), 1489 (w), 1460 (w), 1443 (m), 1363 (w), 1305 (m), 1283 (m), 1258 (s), 1151 (w), 1095 (m), 1017 (m), 962 (m), 867 (w), 800 (w).

Analysis: Calcd for $C_{18}H_{16}O_6$: C, 65.85%; H, 4.91%. Found: C, 65.56%; H, 4.84%.

Methyl (1*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*)-1,4,4a,9a-tetrahydro-9-hydroxy-6-methoxy-10-methyl-3-oxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



137 **155**

The ketone **137** (400 mg, 1.2 mmol) was dissolved in a 1:1 solution of dichloromethane/methanol (20 ml). Sodium borohydride (46 mg, 1.2 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. Acetone (2 ml) was added to decompose the excess borohydride. The solvent was removed under reduced pressure and the residue was redissolved in ethyl acetate (100 ml). The solution was acidified with 2M HCl (10 ml) and washed with water (20 ml), brine (20 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the alcohol **155** (342 mg, 85%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.22 (1H, d, $J_{8,7}$ = 8.3 Hz, H-8), 6.85 (1H, dd, $J_{7,8}$ = 8.3 Hz, $J_{7,5}$ = 2.3 Hz, H-7), 6.80 (1H, d, $J_{5,7}$ = 2.3 Hz, H-5), 6.04 (1H, d, $J_{11,1}$ = 4.4 Hz, H-11), 5.33 (1H, d, $J_{9,9a}$ = 8.4 Hz, H-9), 5.31 (1H, dd, $J_{1,9a}$ = 4.1 Hz, $J_{1,11}$ = 4.5 Hz, H-1), 4.34 (1H, d, $J_{4a,9a}$ = 8.1 Hz, H-4a), 4.03 (3H, s, COO**CH_3**), 3.77 (3H, s, **CH_3**O-C6),

3.52 (1H, ddd, $J_{9a,4a}$ = 8.1 Hz, $J_{9a,1}$ = 3.8 Hz, $J_{9a,9}$ = 8.4 Hz, H-9a), 1.63 (3H, s, **CH_3**-C10).

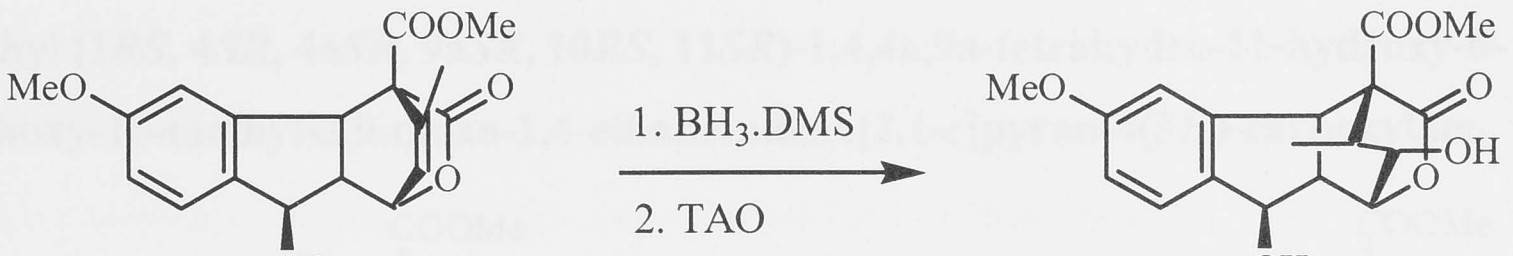
^{13}C-NMR (75MHz, $CDCl_3$): δ 171.67 (C3), 169.12 (C12), 161.03 (C6), 140.79 (C4b), 140.52 (C10), 138.31 (C8a), 125.98 (C8), 125.50 (C11), 115.65 (C5), 110.36 (C7), 75.26 (C1), 73.80 (C9), 64.49 (C4), 56.01 (**CH_3**O-C6), 53.47 (COO**CH_3**), 49.31 (C9a), 46.83 (C4a), 20.81 (**CH_3**-C10).

LRMS (*m/z*): 330 (M^+, 24%), 300 (1), 286 (17), 268 (9), 254 (45), 236 (14), 225 (71), 209 (59), 195 (17), 184 (10), 175 (58), 162 (100), 147 (42), 135 (54), 119 (15), 102 (15), 91 (21), 77 (17), 65 (12).

HRMS (EI): Found 330.1106 (M^+), $C_{18}H_{18}O_6$ requires 330.1103.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3486 (br), 3012 (w), 2953 (w), 2837 (w), 1749 (s), 1607 (m), 1496 (m), 1444 (w), 1380 (w), 1366 (w), 1301 (m), 1273 (s), 1199 (w), 1159 (w), 1102 (m), 1078 (m), 954 (w), 822 (w), 699 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-1,4,4a,9a-tetrahydro-9,11-dihydroxy-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



155 **153**

2M Borane-dimethyl sulfide in tetrahydrofuran (2 ml, 4 mmol) was added dropwise over 5 minutes to the alkene **155** (815 mg, 2.47 mmol) in tetrahydrofuran (25 ml) at 0°C. Stirring was continued at room temperature for 10 hours. Triethylamine *N*-oxide (900 mg, 8.1 mmol) was added and the mixture was heated under for 16 hours. The solution was filtered through a short pad of silica gel and the solvent was removed under vacuum. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 1:1) to afford the alcohol **153** (423 mg, 49%) as a colourless oil and starting material (80 mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.29 (1H, d, $J_{8,7}$ = 8.7 Hz, H-8), 6.92 (1H, dd, $J_{7,8}$ = 8.7 Hz, $J_{7,5}$ = 1.7 Hz, H-7), 6.85 (1H, d, $J_{5,7}$ = 1.7 Hz, H-5), 5.50 (1H, d, $J_{9,9a}$ = 9.5 Hz, H-9), 4.94 (1H, d, $J_{1,9a}$ = 4.2 Hz, H-1), 4.13 (1H, d, $J_{4a,9a}$ = 9.9 Hz, H-4a), 4.08 (1H, d, $J_{11,10}$ = 5.5 Hz, H-11), 3.96 (3H, s, COO**CH$_3$**), 3.77 (3H, s, **CH$_3$**O-C6), 3.31 (1H, ddd, $J_{9a,4a}$ = 9.9 Hz, $J_{9a,1}$ = 4.2 Hz, $J_{9a,9}$ = 9.5 Hz, H-9a), 2.31 (1H, dq, $J_{10,Me}$ = 7.2 Hz, $J_{10,11}$ = 5.5 Hz, H-10), 0.60 (3H, d, $J_{Me,10}$ = 7.2 Hz, **CH$_3$**-C10).

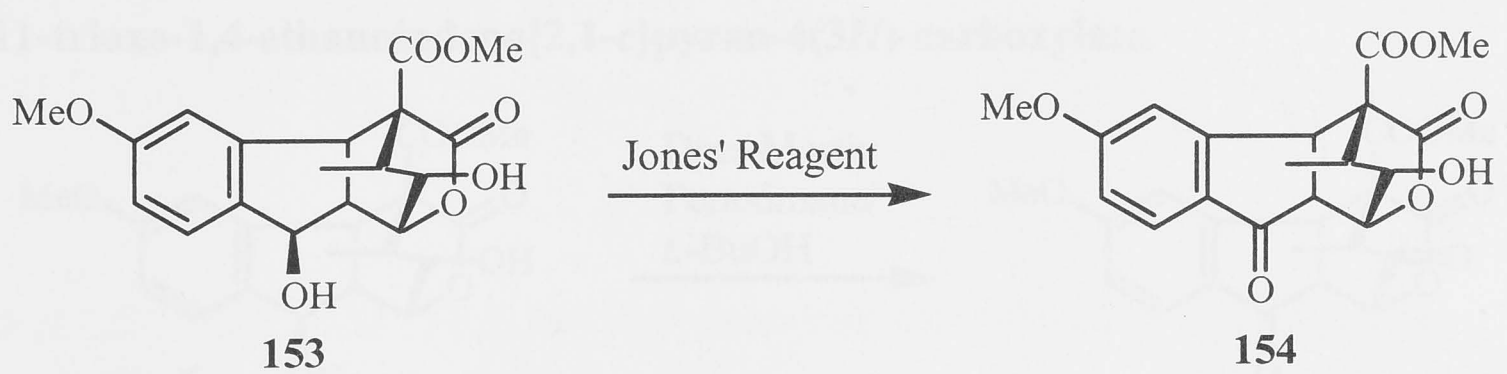
^{13}C-NMR (75MHz, $CDCl_3$): δ 173.54 (C3), 170.02 (C12), 161.01 (C6), 141.27 (C4b), 136.59 (C8a), 126.52 (C8), 116.21 (C5), 112.06 (C7), 83.19 (C11), 73.69 (C9), 72.49 (C1), 59.27 (C4), 56.04 (**CH$_3$**O-C6), 53.50 (COO**CH$_3$**), 44.85 (C9a), 42.29 (C4a), 41.98 (C10), 16.53 (**CH$_3$**-C10).

LRMS (*m/z*): 348 (M^+, 100%), 330 (25), 317 (10), 299 (8), 271 (19), 258 (29), 241 (46), 227 (49), 211 (34), 199 (22), 185 (30), 175 (59), 158 (32), 145 (42), 127 (24), 115 (28), 102 (12), 91 (12), 77 (12), 59 (11).

HRMS (EI): Found 348.1207 (M^+), $C_{18}H_{20}O_7$ requires 348.1209.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3445 (br), 3010 (w), 2951 (w), 1738 (s), 1607 (m), 1494 (m), 1436 (w), 1271 (m), 1151 (w), 1114 (m), 1034 (m), 989 (w), 871 (w), 735 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*RS*, 11*SR*)-1,4,4a,9a-tetrahydro-11-hydroxy-6-methoxy-10-methyl-3,9-dioxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



153 **154**

Jones' reagent was added dropwise to the diol **153** (20 mg, 0.057 mmol) in acetone (1ml) until an orange colour persisted. The solution was stirred for 1 hour and isopropyl alcohol (1 ml) was added. The solution was filtered through a short pad of silica gel and the solvent was then removed under reduced pressure. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the ketone **154** (11 mg, 55%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.72 (1H, d, $J_{8,7}$ = 8.7 Hz, H-8), 7.16 (1H, d, $J_{5,7}$ = 2.0 Hz, H-5), 7.02 (1H, dd, $J_{7,8}$ = 8.7 Hz, $J_{7,5}$ = 2.0 Hz, H-7), 5.06 (1H, d, $J_{1,9a}$ = 5.3 Hz, H-1), 4.30 (1H, d, $J_{4a,9a}$ = 8.4 Hz, H-4a), 3.96 (3H, s, COO**CH$_3$**), 3.87 (3H, s, **CH$_3$**O-C6), 3.51 (1H, d, $J_{11,10}$ = 5.0 Hz, H-11), 3.47 (1H, dd, $J_{9a,4a}$ = 8.4 Hz, $J_{9a,1}$ = 5.3 Hz, H-9a), 2.46 (1H, dq, $J_{10,Me}$ = 7.3 Hz, $J_{10,11}$ = 5.0 Hz, H-10), 0.48 (3H, d, $J_{Me,10}$ = 7.3 Hz, **CH$_3$**-C10).

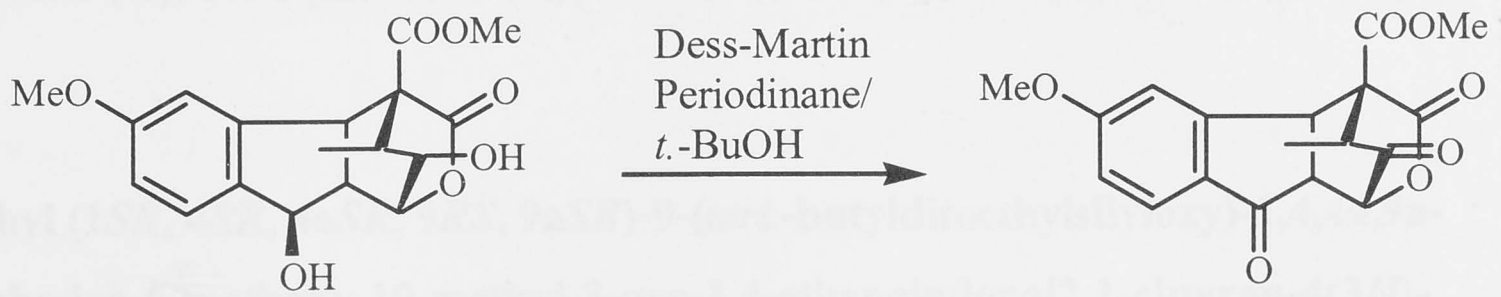
^{13}C-NMR (75MHz, $CDCl_3$): δ 200.44 (C9), 172.20 (C3), 169.73 (C12), 166.89 (C6), 157.08 (C4b), 130.83 (C8a), 127.25 (C8), 117.83 (C5), 112.36 (C7), 82.09 (C11), 71.90 (C1), 59.53 (C4), 56.47 (**CH$_3$**O-C6), 53.71 (COO**CH$_3$**), 50.54 (C9a), 41.62 (C10), 39.06 (C4a), 16.40 (**CH$_3$**-C10).

LRMS (*m/z*): 346 (M^+, 100%), 314 (26), 302 (5), 286 (11), 269 (18), 247 (23), 225 (100), 211 (27), 200 (12), 187 (18), 174 (19), 161 (29), 145 (11), 128 (13), 115 (18), 102 (11), 84 (10), 77 (12), 63 (11).

HRMS (EI): Found 346.1049 (M^+), $C_{18}H_{18}O_7$ requires 346.1053.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3481 (br), 2950 (w), 1761 (s), 1744 (s), 1703 (s), 1595 (s), 1489 (w), 1439 (w), 1340 (w), 1309 (w), 1295 (s), 1150 (w), 1103 (m), 1033 (m), 972 (w), 912 (w), 875 (w), 733 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*RS*)-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-3,9,11-trioxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



153 **154**

tert.-Butyl alcohol (990 μl, 10.34 mmol) was added to the Dess Martin periodinane (2.14 g, 5.17 mmol) in tetrahydrofuran (50 ml) and the solution was stirred for 20 minutes. The diol **153** (600 mg, 1.72 mmol) in tetrahydrofuran (5 ml) was added via syringe over 10 minutes. The solution was stirred for a further 2 hours at room temperature. A 1:1 mixture of saturated aqueous sodium thiosulfate and sodium

bicarbonate (20 ml) was added and stirring was continued for 20 minutes. The product was extracted with ethyl acetate (3x50 ml) and the combined organic phase was washed with saturated sodium thiosulfate (20 ml) and brine (20 ml). After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the diketone **154** (285 mg, 48%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.15 (1H, d, $J_{8,7}$ = 8.6 Hz, H-8), 7.07 (1H, d, $J_{5,7}$ = 2.1 Hz, H-5), 7.01 (1H, dd, $J_{7,8}$ = 8.6 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 5.09 (1H, d, $J_{1,9a}$ = 5.4 Hz, H-1), 4.55 (1H, d, $J_{4a,9a}$ = 8.7 Hz, H-4a), 4.03 (3H, s, COO**CH$_3$**), 3.87 (3H, s, **CH$_3$**O-C6), 3.71 (1H, dd, $J_{9a,4a}$ = 8.7 Hz, $J_{9a,1}$ = 5.4 Hz, H-9a), 3.17 (1H, q, $J_{10,Me}$ = 7.3 Hz, H-10), 0.49 (3H, d, $J_{Me,10}$ = 7.3 Hz, **CH$_3$**-C10).

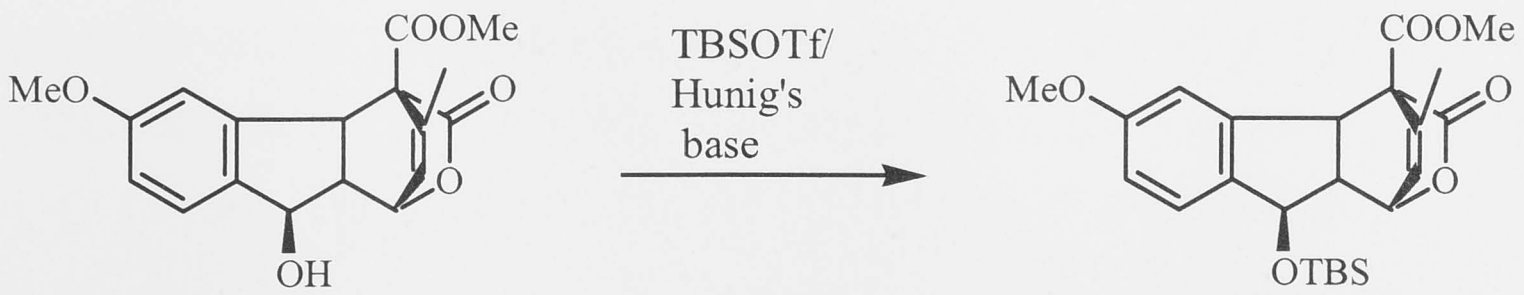
^{13}C-NMR (75MHz, $CDCl_3$): δ 203.20 (C11), 196.45 (C9), 170.01 (C3), 168.07 (C12), 166.93 (C6), 154.65 (C4b), 131.02 (C8a), 127.54 (C8), 117.98 (C5), 112.22 (C7), 81.89 (C1), 60.16 (C4), 56.52 (**CH$_3$**O-C6), 54.13 (COO**CH$_3$**), 51.58 (C9a), 44.36 (C10), 39.41 (C4a), 12.45 (**CH$_3$**-C10).

LRMS (*m/z*): 344 (M^+, 100%), 312 (33), 300 (3), 285 (6), 268 (17), 257 (61), 248 (33), 241 (53), 229 (27), 213 (21), 200 (27), 190 (39), 174 (16), 161 (37), 145 (12), 127 (74), 115 (21), 102 (15), 89 (10), 77 (13), 59 (19).

HRMS (EI): Found 344.0898 (M^+), $C_{18}H_{20}O_7$ requires 344.0896.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3006 (w), 2950 (w), 2889 (w), 1772 (s), 1741 (s), 1709 (s), 1598 (s), 1492 (m), 1454 (w), 1438 (m), 1380 (w), 1335 (m), 1304 (s), 1258 (s), 1207 (w), 1152 (w), 1098 (m), 1065 (m), 1023 (m), 971 (w), 846 (w), 817 (w), 661 (w).

Methyl (1*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*SR*)-9-(*tert.*-butyldimethylsilyloxy)-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-3-oxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



155 **156**

tert.-Butyldimethylsilyl trifluoromethanesulfonate (112 µl, 0.49 mmol) was added dropwise over 10 minutes to the alcohol **155** (108 mg, 0.327 mmol) and *N,N*-diisopropylethylamine (170 µl, 0.98 mmol) in dichloromethane (10 ml). Stirring was continued at room temperature for 1.5 hours. The mixture was filtered though a short pad of silica gel and the solvent was removed under reduced pressure. The residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 10:1) to yield the ether **156** (110 mg, 76%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.07 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.81 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 6.75 (1H, d, $J_{5,7}$ = 2.1 Hz, H-5), 5.92 (1H, d, $J_{11,1}$ = 5.1 Hz, H-11), 5.25 (1H, d, $J_{9,9a}$ = 8.5 Hz, H-9), 5.16 (1H, dd, $J_{1,9a}$ = 3.7 Hz, $J_{1,11}$ = 5.1 Hz, H-1), 4.31 (1H, d, $J_{4a,9a}$ = 7.8 Hz, H-4a), 4.01 (3H, s, COO**CH$_3$**), 3.75 (3H, s, **CH$_3$**O-C6), 3.40 (1H, ddd, $J_{9a,4a}$ = 8.1 Hz, $J_{9a,1}$ = 3.6 Hz, $J_{9a,9}$ = 8.2 Hz, H-9a), 1.57 (3H, s, **CH$_3$**-C10), 0.98 (9H, s, **(CH$_3$)$_3$**-C), 0.23 (3H, s, **CH$_3$**-Si), 0.22 (3H, s, **CH$_3$**-Si).

^{13}C-NMR (75MHz, $CDCl_3$): δ 171.15 (C3), 168.77 (C12), 159.98 (C6), 139.37 (C4b), 139.03 (C10), 137.98 (C8a), 125.15 (C8), 125.05 (C11), 114.82 (C5), 109.57 (C7), 75.30 (C1), 73.53 (C9), 63.99 (C4), 55.47 (COO**CH$_3$**), 52.89 (**CH$_3$**O-C6), 48.63 (C9a), 46.83 (C4a), 25.92 (**(CH$_3$)$_3$**-C), 20.23 (**CH$_3$**-C10), 18.18 ((CH$_3$)$_3$-**C**), -4.49 (**CH$_3$**-Si), -4.53 (**CH$_3$**-Si).

LRMS (*m/z*): 444 (M^+, 8%), 385 (3), 343 (33), 313 (14), 276 (32), 238 (17), 229 (21), 219 (33), 209 (40), 193 (21), 179 (15), 163 (21), 145 (100), 102 (9), 89 (26), 73 (72), 54 (29).

HRMS (EI): Found 444.1965 (M^+), $C_{24}H_{32}O_6Si$ requires 444.1968.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3065 (w), 2998 (w), 2954 (m), 2930 (w), 2857 (w), 1757 (s), 1606 (m), 1496 (m), 1476 (m), 1444 (w), 1378 (w), 1363 (w), 1319 (w), 1274 (m), 1259 (m), 1156 (w), 1108 (m), 1082 (m), 1025 (w), 1004 (w), 959 (w), 855 (w), 838 (w), 777 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*SR*, 10*RS*, 11*SR*)-9-(*tert.*-butyldimethylsilyloxy)-1,4,4a,9a-tetrahydro-11-hydroxy-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.

156 **157**

2M Borane-dimethyl sulfide in tetrahydrofuran (198 µl, 0.396 mmol) was added to the alkene **156** (160 mg, 0.36 mmol) in tetrahydrofuran (10 ml). Stirring was continued at room temperature for 14 hours. Triethylamine oxide (240 mg, 2.16 mmol) was added and the mixture was refluxed for 16 hours. The solution was filtered through a short pad of silica gel and the solvent was removed under reduced vacuum. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 4:1) to afford the alcohol **157** (85 mg, 51%) as a colourless oil and starting material (10 mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.17 (1H, d, $J_{8,7}$ = 8.7 Hz, H-8), 6.89 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 1.8 Hz, H-7), 6.84 (1H, d, $J_{5,7}$ = 1.8 Hz, H-5), 5.37 (1H, d, $J_{9,9a}$ = 9.6 Hz, H-9), 4.73 (1H, d, $J_{1,9a}$ = 4.0 Hz, H-1), 4.11 (1H, d, $J_{4a,9a}$ = 9.6 Hz, H-4a), 4.01 (1H, d, $J_{11,10}$ = 5.6 Hz, H-11), 3.95 (3H, s, COO**CH$_3$**), 3.75 (3H, s, **CH$_3$**O-C6), 3.24 (1H, ddd, $J_{9a,4a}$ = 9.7 Hz, $J_{9a,1}$ = 4.1 Hz, $J_{9a,9}$ = 9.7 Hz, H-9a), 2.27 (1H, dq, $J_{10,Me}$ = 7.3 Hz, $J_{10,11}$ = 5.6 Hz, H-10), 0.98 (9H, s, **(CH$_3$)$_3$**-C), 0.55 (3H, d, $J_{Me,10}$ = 7.2 Hz, **CH$_3$**-C10), 0.25 (3H, s, **CH$_3$**-Si), 0.22 (3H, s, **CH$_3$**-Si).

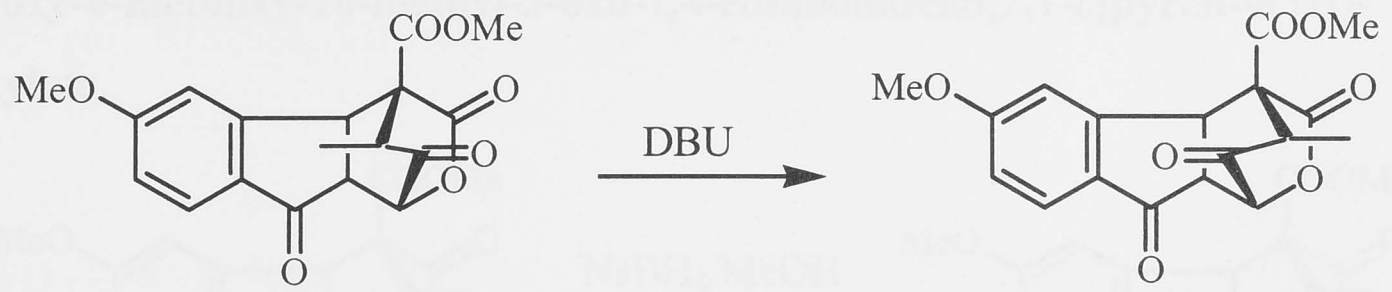
^{13}C-NMR (75MHz, $CDCl_3$): δ 172.78 (C3), 169.72 (C12), 160.49 (C6), 140.26 (C4b), 136.86 (C8a), 125.94 (C8), 115.88 (C5), 111.66 (C7), 83.18 (C11), 73.85 (C9), 72.03 (C1), 59.04 (C4), 55.70 (COO**CH$_3$**), 53.07 (**CH$_3$**O-C6), 44.72 (C9a), 42.09 (C4a), 41.76 (C10), 26.04 (**(CH$_3$)$_3$**-C), 18.31 ((CH$_3$)$_3$-**C**), 16.12 (**CH$_3$**-C10), -4.35 (**CH$_3$**-Si), -4.46 (**CH$_3$**-Si).

LRMS (*m/z*): 462 (M^+, 46%), 431 (6), 405 (29), 397 (15), 345 (10), 331 (35), 317 (68), 313 (32), 300 (32), 285 (44), 257 (67), 237 (16), 227 (19), 225 (33), 209 (22), 197 (31), 185 (31), 159 (44), 145 (100), 125 (18), 115 (17), 85 (51), 75 (93), 57 (42).

HRMS (EI): Found 462.2080 (M^+), $C_{24}H_{34}O_7Si$ requires 462.2074.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3496 (br), 2998 (w), 2952 (m), 2931 (m), 2857 (w), 2885 (w), 1758 (s), 1606 (m), 1492 (m), 1463 (w), 1435 (w), 1364 (w), 1327 (m), 1260 (m), 1150 (w), 1115 (m), 1083 (w), 1037 (m), 992 (w), 862 (w), 776 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*SR*)-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-3,9,11-trioxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



150 **152**

DBU (10 µl, 0.07) was added to a solution of diketone **150** (200 mg, 0.58 mmol) in tetrahydrofuran (20 ml) and stirred for 16 hours. The solvent was removed under reduced pressure and the residue was chromatographed using MPLC (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the epimer **152** (144 mg, 72%) as a colourless oil and starting material (41 mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.73 (1H, d, $J_{8,7}$ = 8.7 Hz, H-8), 7.04 (1H, dd, $J_{7,8}$ = 8.7 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.59 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 4.96 (1H, d, $J_{1,9a}$ = 5.1 Hz, H-1), 4.54 (1H, d, $J_{4a,9a}$ = 8.4 Hz, H-4a), 4.05 (3H, s, COO**CH_3**), 3.88 (3H, s, **CH_3**O-C6), 3.70 (1H, dd, $J_{9a,4a}$ = 8.4 Hz, $J_{9a,1}$ = 5.1 Hz, H-9a), 2.34 (1H, q, $J_{10,Me}$ = 7.4 Hz, H-10), 1.35 (3H, d, $J_{Me,10}$= 7.4 Hz, **CH_3**-C10).

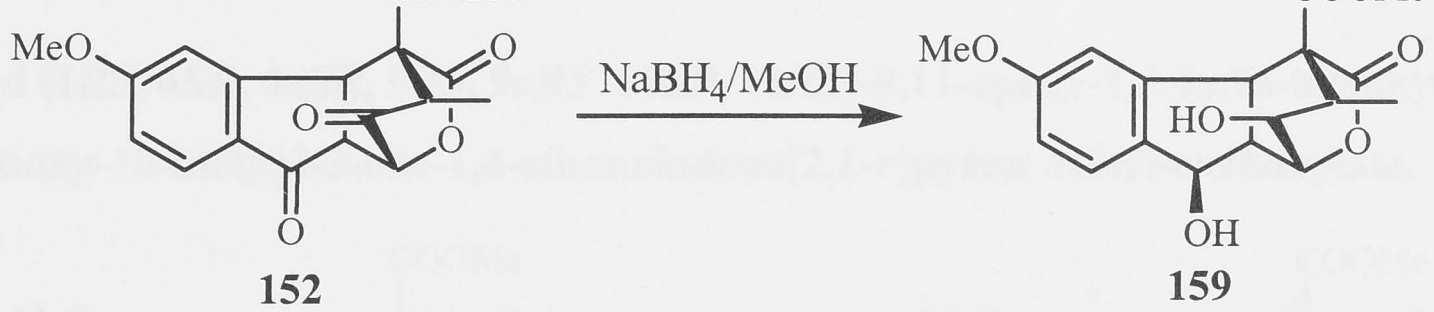
^{13}C-NMR (75MHz, $CDCl_3$): δ 203.14 (C11), 196.14 (C9), 168.13 (C3), 168.10 (C12), 167.04 (C6), 152.31 (C4b), 131.14 (C8a), 127.67 (C8), 117.79 (C5), 110.32 (C7), 82.05 (C1), 58.37 (C4), 56.46 (**CH_3**O-C6), 53.93 (COO**CH_3**), 50.50 (C9a), 42.68 (C10), 42.42 (C4a), 14.72 (**CH_3**-C10).

LRMS (*m/z*): 344 (M^+, 100%), 312 (22), 299 (2), 285 (4), 268 (7), 257 (70), 241 (28), 229 (26), 213 (13), 200 (26), 190 (54), 174 (13), 161 (35), 145 (11), 127 (82), 115 (15), 95 (10), 77 (8), 59 (13).

HRMS (EI): Found 344.0895 (M^+), $C_{18}H_{20}O_7$ requires 344.0896.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3005 (w), 2955 (w), 2848 (w), 1773 (s), 1741 (s), 1705 (s), 1595 (s), 1490 (m), 1458 (w), 1438 (m), 1383 (w), 1335 (m), 1304 (s), 1258 (s), 1208 (w), 1149 (w), 1098 (m), 1065 (m), 1021 (m), 970 (w), 877 (w), 849 (w), 816 (w), 734 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-1,4,4a,9a-tetrahydro-9,11-dihydroxy-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



152 **159**

Sodium borohydride (109 mg, 2.87 mmol) was added to the diketone **152** (330 mg, 0.96 mmol) in a 10:1 solution of tetrahydrofuran/methanol (20 ml) and stirred for 6 hours. The solution was acidified with 2M HCl (10 ml) and extracted with ethyl acetate (3x80 ml). The combined organic phase was washed with brine (30 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 1:1) to afford the diol **159** (221 mg, 66%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.35 (1H, d, $J_{8,7}$ = 8.3 Hz, H-8), 6.92 (1H, dd, $J_{7,8}$ = 8.3 Hz, $J_{7,5}$ = 1.9 Hz, H-7), 6.44 (1H, d, $J_{5,7}$ = 1.9 Hz, H-5), 5.35 (1H, d, $J_{9,9a}$ = 9.9 Hz, H-9), 4.92 (1H, d, $J_{1,9a}$ = 3.8 Hz, H-1), 4.13 (1H, d, $J_{4a,9a}$ = 10.3 Hz, H-4a), 3.96 (3H, s, COO**CH_3**), 3.78 (3H, s, **CH_3**O-C6), 3.77 (1H, d, $J_{11,10}$ = 3.4 Hz, H-11), 3.49 (1H, ddd, $J_{9a,4a}$ = 10.3 Hz, $J_{9a,1}$ = 3.8 Hz, $J_{9a,9}$ = 9.9 Hz, H-9a), 2.04 (1H, dq, $J_{10,Me}$ = 7.0 Hz, $J_{10,11}$ = 3.4 Hz, H-10), 1.27 (3H, d, $J_{Me,10}$ = 7.0 Hz, **CH_3**-C10).

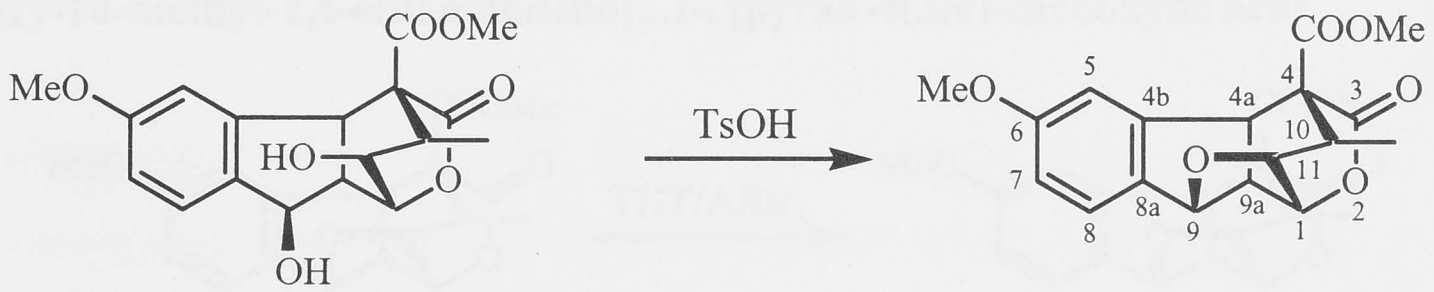
^{13}C-NMR (75MHz, $CDCl_3$): δ 169.98 (C3), 169.43 (C12), 161.23 (C6), 138.93 (C4b), 138.61 (C8a), 126.11 (C8), 115.75 (C5), 110.02 (C7), 78.64 (C11), 74.34 (C9), 74.26 (C1), 60.99 (C4), 55.93 (**CH_3**O-C6), 53.40 (COO**CH_3**), 45.98 (C9a), 45.59 (C4a), 38.34 (C10), 14.76 (**CH_3**-C10).

LRMS (*m/z*): 348 (M^+, 100%), 330 (48), 317 (6), 299 (13), 271 (11), 258 (24), 253 (25), 241 (36), 225 (41), 213 (19), 202 (21), 186 (39), 175 (62), 162 (38), 145 (52), 127 (47), 115 (31), 102 (15), 96 (15), 77 (16), 59 (13).

HRMS (EI): Found 348.1207 (M^+), $C_{18}H_{20}O_7$ requires 348.1209.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3392 (br), 2953 (w), 2849 (w), 1763 (m), 1732 (s), 1710 (m), 1597 (s), 1490 (w), 1462 (w), 1437 (w), 1338 (w), 1307 (w), 1260 (s), 1149 (w), 1099 (w), 1030 (w), 913 (w), 842 (w), 803 (w), 731 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



159 **162**

The diol **159** (210 mg, 60 mmol) and *p*-toluenesulfonic acid (115 mg, 60 mmol) were dissolved in tetrahydrofuran (20 ml) and stirred for 2 hours. The solution was filtered through a short pad of silica gel and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the ether **162** (142 mg, 71%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.33 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 6.86 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 1.9 Hz, H-7), 6.48 (1H, d, $J_{5,7}$ = 1.9 Hz, H-5), 5.22 (1H, d, $J_{9,9a}$ = 5.0 Hz, H-9), 5.15 (1H, dd, $J_{1,9a}$ = 5.6 Hz, $J_{1,11}$ = 5.7 Hz, H-1), 4.10 (1H, d, $J_{4a,9a}$ = 8.8 Hz, H-4a), 3.96 (1H, d, $J_{11,1}$ = 5.7 Hz, H-11), 3.93 (3H, s, COO**CH_3**), 3.78 (3H, s, **CH_3**O-C6), 3.57 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.6 Hz, $J_{9a,9}$ = 5.0 Hz, H-9a), 2.16 (1H, q, $J_{10,Me}$ = 7.5 Hz, H-10), 1.10 (3H, d, $J_{Me,10}$ = 7.5 Hz, **CH_3**-C10).

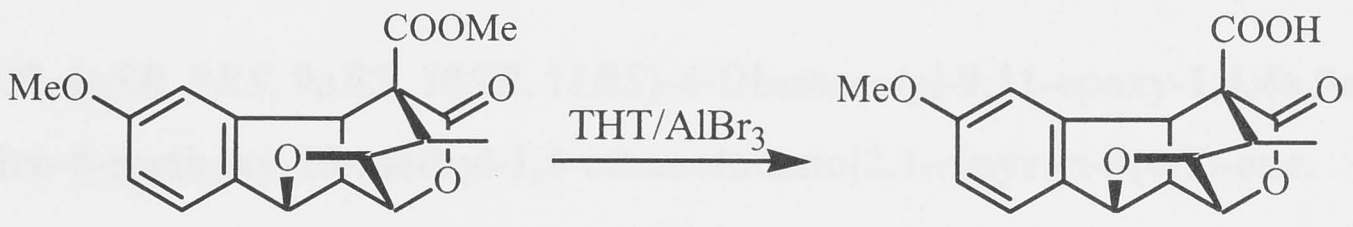
^{13}C-NMR (75MHz, $CDCl_3$): δ 169.04 (C3), 168.36 (C12), 161.40 (C6), 141.85 (C4b), 136.80 (C8a), 126.48 (C8), 115.33 (C5), 110.20 (C7), 82.79 (C11), 79.66 (C1), 79.58 (C9), 57.55 (C4), 55.63 (**CH_3**O-C6), 52.69 (COO**CH_3**), 49.23 (C9a), 45.86 (C4a), 37.42 (C10), 17.36 (**CH_3**-C10).

LRMS (*m/z*): 330 (M^+, 100%), 299 (6), 271 (8), 241 (15), 226 (4), 214 (11), 197 (10), 186 (62), 175 (22), 158 (15), 146 (39), 127 (58), 115 (21), 102 (15), 89 (3), 77 (5), 59 (9).

HRMS (EI): Found 330.1104 (M^+), $C_{18}H_{18}O_6$ requires 330.1103.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2998 (w), 2951 (m), 2879 (w), 2838 (w), 1766 (s), 1744 (s), 1608 (m), 1495 (m), 1465 (w), 1435 (w), 1373 (w), 1341 (w), 1311 (m), 1295 (m), 1258 (s), 1213 (w), 1147 (m), 1103 (m), 1087 (s), 1057 (m), 1016 (w), 998 (w), 913 (w), 825 (w), 729 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylic acid.



162 **163**

Tetrahydrothiophene (320 µl, 3.64 mmol) was added to a solution of aluminum tribromide (194 mg, 0.728 mmol) in dichloromethane (10 ml) at 0°C. The mixture was stirred for 5 minutes and the ester **162** (120 mg, 0.364 mmol) in dichloromethane (2 ml) was then added dropwise over 10 minutes. Stirring was continued for 20 hours at room temperature. 4M HCl (10 ml) was added and the product was extracted with dichloromethane (4x50 ml). The combined organic phase was washed with brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate : acetic acid = 1:2:0.03) to afford the acid **163** (79 mg, 69%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.33 (1H, d, $J_{8,7}$ = 8.2 Hz, H-8), 6.86 (1H, dd, $J_{7,8}$ = 8.2 Hz, $J_{7,5}$ = 1.9 Hz, H-7), 6.72 (1H, d, $J_{5,7}$ = 1.9 Hz, H-5), 5.24 (1H, d, $J_{9,9a}$ = 5.2 Hz, H-9), 5.20 (1H, dd, $J_{1,9a}$ = 5.6 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 4.03 (1H, d, $J_{4a,9a}$ = 8.7 Hz, H-4a), 4.01 (1H, d, $J_{11,1}$ = 5.6 Hz, H-11), 3.76 (3H, s, **CH_3**O-C6), 3.62 (1H, ddd, $J_{9a,4a}$ = 8.7 Hz, $J_{9a,1}$ = 5.6 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.21 (1H, q, $J_{10,Me}$ = 7.4 Hz, H-10), 1.10 (3H, d, $J_{Me,10}$ = 7.4 Hz, **CH_3**-C10).

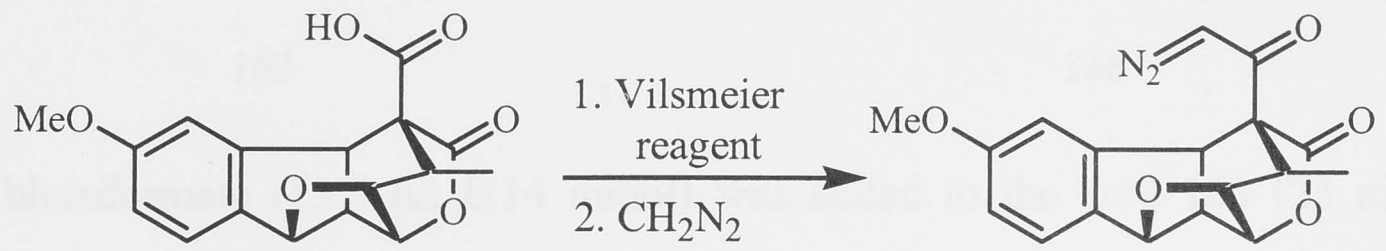
^{13}C-NMR (75MHz, $CDCl_3$): δ 171.42 (C12), 170.76 (C3), 161.46 (C6), 141.25 (C4b), 136.46 (C8a), 126.39 (C8), 116.32 (C5), 110.55 (C7), 82.74 (C11), 79.84 (C1), 79.21 (C9), 56.99 (C4), 55.74 (**CH_3**O-C6), 49.23 (C9a), 46.29 (C4a), 37.64 (C10), 17.12 (**CH_3**-C10).

LRMS (*m/z*): 316 (M^+, 100%), 272 (2), 244 (3), 226 (7), 213 (5), 197 (12), 186 (31), 175 (48), 158 (9), 146 (25), 128 (6), 115 (16), 102 (12), 89 (2), 77 (5).

HRMS (EI): Found 316.0944 (M^+), $C_{17}H_{16}O_6$ requires 316.0947.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3500 (br), 2957 (w), 2951 (w), 1764 (s), 1607 (m), 1495 (m), 1464 (w), 1373 (w), 1345 (w), 1302 (w), 1261 (m), 1241 (w), 1215 (w), 1149 (m), 1120 (w), 1089 (m), 1054 (m), 996 (w), 826 (w), 734 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-Diazoacetyl-9,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



163 **164**

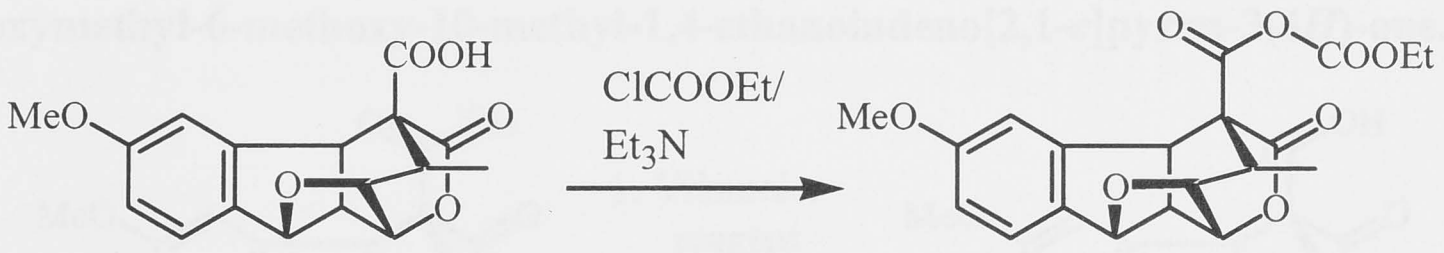
Oxalyl chloride (95 µl, 1.09 mmol) was added to the acid **163** (72 mg, 0.218 mmol) and pyridine (123 µl, 1.527 mmol) in dry ether (20 ml). A few drops of DMF were added and stirring was continued under nitrogen for 1.5 hours. The mixture was filtered though celite and washed with ether (5 ml). Toluene (10 ml) was added and removed under reduced pressure. This last step was repeated twice. The acid chloride was dissolved in a 1:1 solution of ether/tetrahydrofuran (5 ml) and then added to an excess of ethereal diazomethane at 0°C. Stirring was continued for 16 hours at room temperature. The mixture was filtered through a short pad of silica gel and the solvent was removed to give diazoketone **164** (41mg, 53%) as a yellow oil which was used in the next step without further purification.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.31 (1H, d, $J_{8,7}$ = 8.3 Hz, H-8), 6.86 (1H, dd, $J_{7,8}$ = 8.3 Hz, $J_{7,5}$ = 2.3 Hz, H-7), 6.48 (1H, d, $J_{5,7}$ = 2.6 Hz, H-5), 6.02 (1H, s (br) C1'-

C**H**N_2), 5.21 (1H, d, $J_{9,9a}$ = 5.2 Hz, H-9), 5.16 (1H, dd, $J_{1,9a}$ = 5.5 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 3.99 (1H, d, $J_{11,1}$ = 5.6 Hz, H-11), 3.77 (3H, s, **CH_3**O-C6), 3.72 (1H, d, $J_{4a,9a}$ = 8.8 Hz, H-4a), 3.57 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.5, Hz, $J_{9a,9}$ = 5.2 Hz, H-9a), 2.33 (1H, q, $J_{10,Me}$ = 7.4 Hz, H-10), 0.93 (3H, d, $J_{Me,10}$ = 7.5 Hz, **CH_3**-C10).

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2960 (w), 2808 (w), 2106 (s), 1757 (s), 1667 (m), 1608 (m), 1494 (w), 1463 (w), 1357 (m), 1298 (w), 1260 (s), 1240 (w), 1189 (m), 1147 (w), 1120 (w), 1086 (m), 1056 (w), 1031 (w), 1014 (w), 918 (w), 801 (m), 769 (w).

Ethoxycarbonyl (1*RS*, 4*RS*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



163 **166**

Ethyl chloroformate (13.5 µl, 0.14 mmol) was added to the acid **163** (23 mg, 0.07 mmol) and triethylamine (24 µl, 0.14 mmol) in dichloromethane (5 ml) and stirred at room temperature for 16 hours. The mixture was filtered though a short pad of silica gel and the solvent was removed under reduced pressure to give anhydride **166** (22 mg, 78%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.31 (1H, d, $J_{8,7}$ = 8.2 Hz, H-8), 6.95 (1H, s, H-5), 6.88 (1H, d, $J_{7,8}$ = 8.1 Hz, H-7), 5.23 (1H, d, $J_{9,9a}$ = 5.6 Hz, H-9), 5.16 (1H, dd, $J_{1,9a}$ = 5.5 Hz, $J_{1,11}$ = 5.8 Hz, H-1), 4.42 (2H, q, $J_{CH2,CH3}$ = 7.0 Hz, **CH_2**CH_3), 4.12 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.97 (1H, d, $J_{11,1}$ = 6.0 Hz, H-11), 3.79 (3H, s, **CH_3**O-C6), 3.60 (1H, ddd, $J_{9a,4a}$ = 8.9 Hz, $J_{9a,1}$ = 5.5 Hz, $J_{9a,9}$ = 5.6 Hz, H-9a), 2.18 (1H, q, $J_{10,Me}$ = 7.3 Hz, H-10), 1.42 (3H, t, $J_{CH3,CH2}$ = 7.0 Hz, CH_2**CH_3**), 1.10 (3H, d, $J_{Me,10}$ = 7.3 Hz, **CH_3**-C10).

^{13}C-NMR (75MHz, $CDCl_3$): δ 169.30 (C3), 165.01 (C12), 163.89 (**C**OOEt), 161.81 (C6), 140.96 (C4b), 136.39 (C8a), 126.43 (C8), 116.90 (C5), 109.70 (C7), 82.80 (C11),

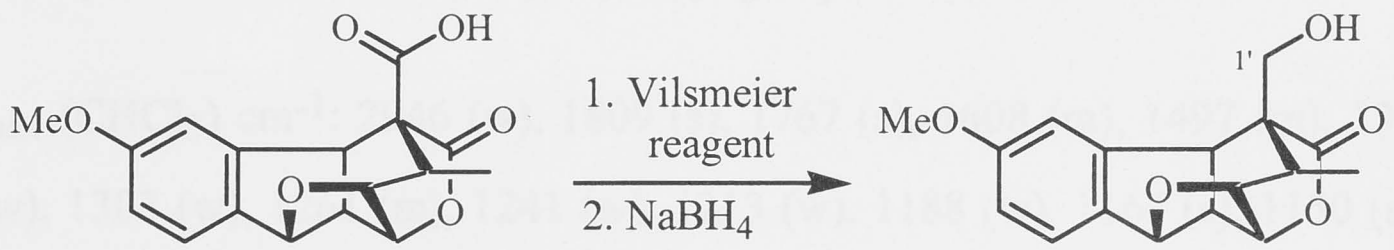
79.74 (C1), 79.32 (C9), 66.88 (O**C**$\mathbf{H_2}$CH$_3$), 57.92 (C4), 55.82 (**C**$\mathbf{H_3}$O-C6), 49.06 (C9a), 45.82 (C4a), 37.42 (C10), 16.93 (**C**$\mathbf{H_3}$-C10), 14.17 (OCH$_2$**C**$\mathbf{H_3}$).

LRMS (*m/z*): 388 (M^+, 100%), 299 (33), 271 (10), 241 (28), 226 (5), 197 (9), 186 (30), 158 (8), 146 (30), 130 (12), 113 (16), 102 (9), 91 (13), 71 (21).

HRMS (EI): Found 388.1155 (M^+), $C_{20}H_{20}O_8$ requires 388.1158.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2946 (w), 1809 (s), 1767 (s), 1608 (m), 1497 (m), 1372 (w), 1344 (w), 1303 (w), 1261 (m), 1241 (w), 1213 (w), 1188 (w), 1164 (s), 1150 (s), 1121 (w), 1081 (s), 1056 (m), 995 (m), 866 (w), 785 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,4,4a,9a-tetrahydro-4-hydroxymethyl-6-methoxy-10-methyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



163 **167**

Oxalyl chloride (194 µl, 2.23 mmol) was added to the acid **163** (140 mg, 0.446 mmol) in dry benzene (25 ml). A few drops of DMF were added and stirring was continued for 2 hours. After removal of the solvent, the residue was dissolved in benzene (10 ml) which was subsequently removed under vacuum. This last step was repeated twice. The residue was redissolved in tetrahydrofuran (15 ml) and cooled to 0°C. A suspension of sodium borohydride (20 mg, 0.535 mmol) in tetrahydrofuran (5 ml) was added over 5 minutes. Stirring was continued for 4 hours at room temperature. Ethyl acetate (100 ml) was added and the mixture was acidified with 2M HCl (10 ml), separated and washed with brine (10 ml). The organic phase was dried over magnesium sulfate, filtered and the solvent was removed. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the alcohol **167** (95 mg, 71%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.32 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.98 (1H, d, $J_{5,7}$ = 2.1 Hz, H-5), 6.85 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 5.22 (1H, d, $J_{9,9a}$ = 5.4 Hz,

H-9), 5.12 (1H, dd, $J_{1,9a}$ = 5.5 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 4.16 (1H, d, J_{gem} = 12.1 Hz, H-1'α), 3.92 (1H, d, $J_{4a,9a}$ = 9.0 Hz, H-4a), 3.84 (1H, d, $J_{11,1}$ = 5.5 Hz, H-11), 3.81 (3H, s, **CH_3**O-C6), 3.54 (1H, ddd, $J_{9a,4a}$ = 9.0 Hz, $J_{9a,1}$ = 5.6, Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 3.38 (1H, d, J_{gem} = 12.1 Hz, H-1'β), 1.61 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.84 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10).

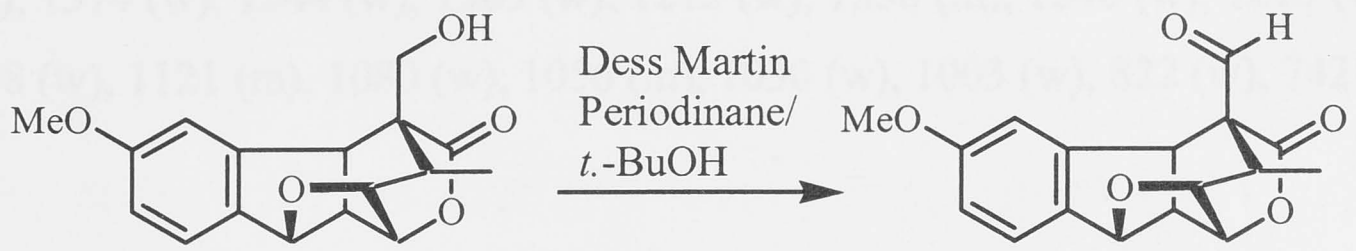
^{13}C-NMR (75MHz, $CDCl_3$): δ 175.71 (C3), 161.38 (C6), 142.82 (C4b), 136.47 (C8a), 126.22 (C8), 115.28 (C5), 111.75 (C7), 83.16 (C11), 79.72 (C1), 79.59 (C9), 60.45 (C1'), 55.79 (**CH_3**O-C6), 50.20 (C4), 46.14 (C9a), 42.25 (C4a), 37.51 (C10), 16.19 (**CH_3**-C10).

LRMS (*m/z*): 302 (M^+, 100%), 284 (1), 255 (6), 243 (4), 227 (9), 216 (7), 199 (11), 188 (21), 175 (37), 159 (58), 139 (39), 128 (13), 115 (31), 99 (23), 77 (9).

HRMS (EI): Found 302.1155 (M^+), $C_{17}H_{18}O_5$ requires 302.1154.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2946 (w), 1809 (s), 1767 (s), 1608 (m), 1497 (m), 1372 (w), 1344 (w), 1303 (w), 1261 (m), 1241 (w), 1213 (w), 1188 (w), 1164 (s), 1150 (s), 1121 (w), 1081 (s), 1056 (m), 995 (m), 866 (w), 785 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-4-formyl-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



167 **168**

tert.-Butyl alcohol (68 μl, 0.714 mmol) was added to the Dess Martin periodinane (171 mg, 0.357 mmol) in tetrahydrofuran (10 ml) and stirred for 5 minutes. The alcohol **167** (72 mg, 0.238 mmol) in tetrahydrofuran (1 ml) was added via syringe over 5 minutes and the solution was stirred for a further 2 hours at room temperature. A 1:1 mixture of saturated aqueous sodium thiosulfate and sodium bicarbonate (5 ml) was added and stirring was continued for 5 minutes. The product was extracted with ethyl acetate (3x30 ml) and the combined organic phase was washed with saturated sodium thiosulfate (10

ml) and brine (10 ml). After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the aldehyde **168** (66 mg, 92%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 10.09 (1H, s, H-1'), 7.31 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.85 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 6.45 (1H, d, $J_{5,7}$ = 2.0 Hz, H-5), 5.23 (1H, d, $J_{9,9a}$ = 5.2 Hz, H-9), 5.17 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 3.99 – 3.94 (2H, m, H-4a, H-11), 3.77 (3H, s, **CH_3**O-C6), 3.64 (1H, ddd, $J_{9a,4a}$ = 8.9 Hz, $J_{9a,1}$ = 5.4, Hz, $J_{9a,9}$ = 5.2 Hz, H-9a), 2.17 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.95 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10).

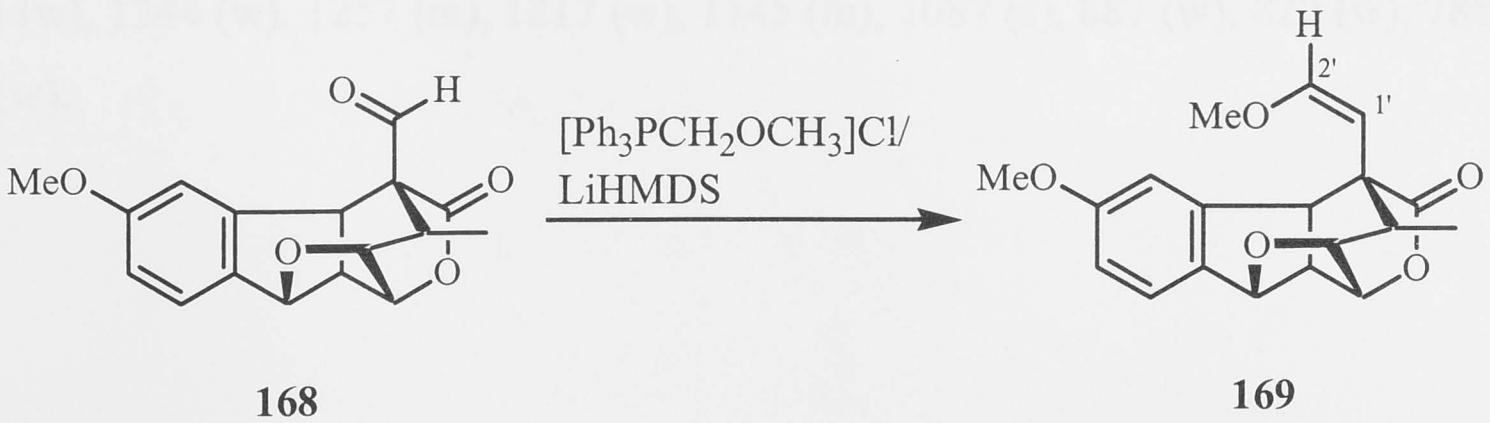
^{13}C-NMR (75MHz, $CDCl_3$): δ 196.88 (C1'), 170.52 (C3), 160.93 (C6), 140.61 (C4b), 136.33 (C8a), 126.23 (C8), 115.61 (C5), 111.50 (C7), 82.48 (C11), 79.45 (C1), 79.04 (C9), 58.55 (C4), 55.56 (**CH_3**O-C6), 46.48 (C9a), 46.09 (C4a), 35.25 (C10), 16.20 (**CH_3**-C10).

LRMS (*m/z*): 300 (M^+, 100%), 272 (14), 254 (6), 243 (20), 226 (24), 213 (19), 197 (35), 186 (25), 175 (21), 159 (21), 145 (39), 127 (15), 115 (37), 97 (32), 77 (11), 57 (12).

HRMS (EI): Found 300.0995 (M^+), $C_{17}H_{16}O_5$ requires 300.0998.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2955 (w), 2838 (w), 1751 (s), 1728 (s), 1607 (m), 1495 (m), 1464 (w), 1374 (w), 1344 (w), 1305 (w), 1275 (w), 1258 (m), 1240 (w), 1213 (w), 1166 (w), 1148 (w), 1121 (m), 1080 (w), 1056 (m), 1030 (w), 1003 (w), 822 (w), 742 (w).

(1*RS*, 4*RS*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,4,4a,9a-tetrahydro-6-methoxy-4-[(Z)-2′-methoxyethenyl]-10-methyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



168 **169**

A 1M solution of lithium hexamethyldisilazide (396 µl, 0.396 mmol) was added dropwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride in dry tetrahydrofuran (8 ml) at room temperature under nitrogen. After 10 minutes, the deep red solution was cooled to 0°C and the aldehyde **168** (66 mg) in tetrahydrofuran (2 ml) was added dropwise over 30 minutes. The mixture was allowed to warm to room temperature and stirred for 1.5 hours. Water (2 ml) was added and stirring was continued for 2 minutes. The solution was acidified with 2M HCl (10 ml) and extracted with ethyl acetate (3x20 ml). The combined organic phase was washed with brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the enol ether **169** (42 mg, 58%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.30 (1H, d, $J_{8,7}$ = 8.7 Hz, H-8), 6.89 – 6.82 (2H, m, H-5, H-7), 6.16 (1H, d, $J_{2',1'}$ = 7.0 Hz, H-2'), 5.20 (1H, d, $J_{9,9a}$ = 5.2 Hz, H-9), 5.07 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 4.35 (1H, d, $J_{1',2'}$ = 6.9 Hz, H-1'), 3.94 (1H, d, $J_{11,1}$ = 5.6 Hz, H-11), 3.81 – 3.77 (4H, m, H-4a, **CH_3**O-C6), 3.52 – 3.48 (4H, m, H-9a, **CH_3**O-C13), 2.14 (1H, q, $J_{10,Me}$ = 7.5 Hz, H-10), 0.89 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10).

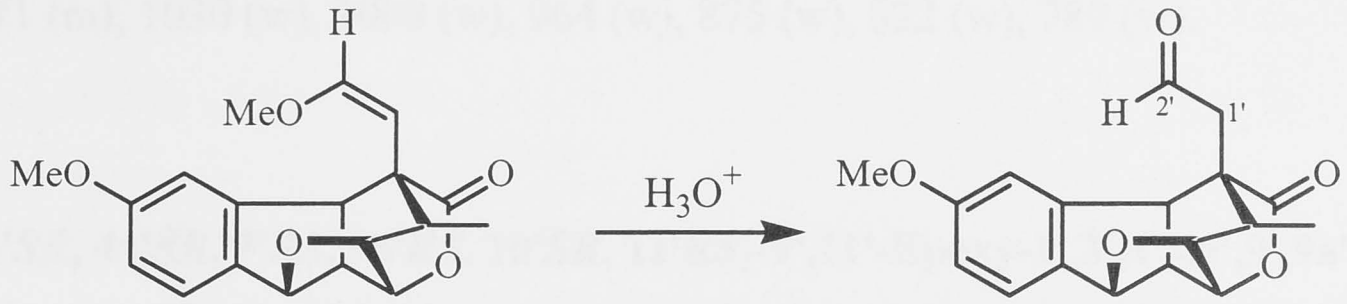
^{13}C-NMR (75MHz, $CDCl_3$): δ 172.76 (C3), 160.66 (C6), 149.71 (C2'), 143.95 (C4b), 137.19 (C8a), 125.60 (C8), 114.10 (C5), 112.99 (C7), 100.21 (C1'), 82.93 (C11), 79.25 (C1), 78.98 (C9), 60.12 (**CH_3**O-C2'), 55.67 (**CH_3**O-C6), 50.53 (C4), 48.42 (C9a), 46.50 (C4a), 39.18 (C10), 16.54 (**CH_3**-C10).

LRMS (*m/z*): 328 (M^+, 64%), 314 (4), 286 (6), 268 (2), 242 (4), 223 (2), 197 (3), 186 (55), 175 (12), 159 (100), 145 (62), 127 (13), 115 (17), 102 (16), 77 (5).

HRMS (EI): Found 328.1309 (M^+), $C_{19}H_{20}O_5$ requires 328.1311.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2937 (w), 1754 (s), 1666 (w), 1607 (m), 1493 (m), 1463 (w), 1374 (w), 1344 (w), 1257 (m), 1217 (w), 1145 (m), 1087 (s), 887 (w), 820 (w), 788 (w), 736 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-4-(2′-oxo-ethyl)-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



169 **170**

The enol ether **169** (30mg, 0.091 mmol), water (500 µl), and HCl (25 µl) were stirred in tetrahydrofuran (2 ml) for 24 hours. The solvent was removed under reduced pressure and the residue was redissolved in ethyl acetate (10 ml). The organic phase was separated, washed with brine (2 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the aldehyde **170** (24 mg, 83%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 10.4 (1H, d, $J_{2',1\beta'}$ = 3.3 Hz, H-2'), 7.33 (1H, d, $J_{8,7}$ = 8.1 Hz, H-8), 6.89 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.87 (1H, dd, $J_{7,8}$ = 8.1 Hz, $J_{7,5}$ = 2.2Hz, H-7), 5.21 (1H, d, $J_{9,9a}$ = 5.4 Hz, H-9), 5.12 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.2 Hz, H-1), 3.93 (1H, d, $J_{11,1}$ = 5.2 Hz, H-11), 3.89 (1H, d, $J_{4a,9a}$ = 8.8 Hz, H-4a), 3.81 (3H, s, **CH_3**O-C6), 3.51 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.2, Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 3.05 (1H, d, J_{gem}= 15.5 Hz, H-1'α), 2.29 (1H, dd, J_{gem}= 15.5 Hz, $J_{1'\beta,2'}$ = 3.3 Hz, H-1'β), 1.68 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.92 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH_3**-C10).

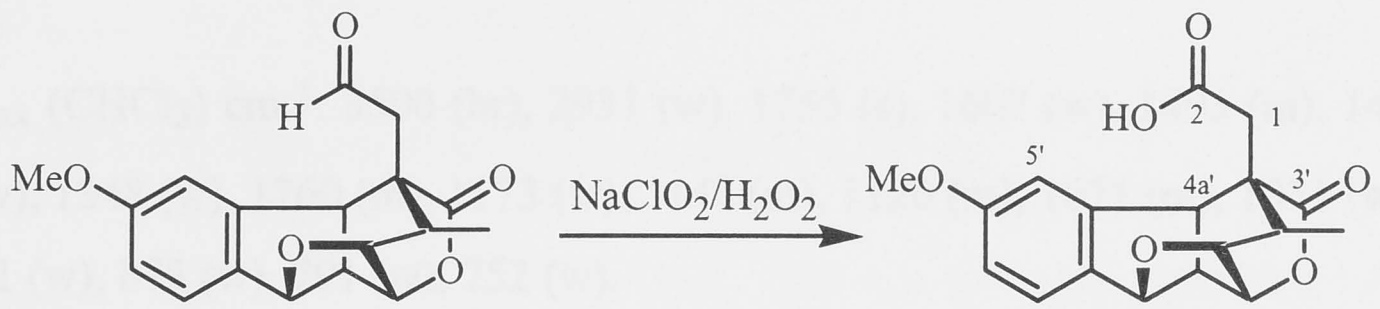
^{13}C-NMR (75MHz, $CDCl_3$): δ 202.20 (C2'), 173.68 (C3), 161.21 (C6), 142.46 (C4b), 137.05 (C8a), 126.45 (C8), 115.36 (C5), 111.85 (C7), 83.02 (C11), 79.72 (C1), 79.32 (C9), 55.75 (**CH_3**O-C6), 48.39 (C9a), 47.39 (C4), 46.13 (C4a), 42.44 (C1'), 40.27 (C10), 16.21 (**CH_3**-C10).

LRMS (*m/z*): 314 (M^+, 24%), 286 (30), 256 (4), 187 (20), 175 (19), 159 (100), 145 (33), 128 (18), 115 (30), 102 (24), 83 (35), 69 (24).

HRMS (EI): Found 314.1151 (M^+), $C_{18}H_{18}O_5$ requires 314.1154.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2959 (w), 2852 (w), 1753 (s), 1717 (s), 1607 (m), 1494 (m), 1465 (w), 1377 (w), 1345 (w), 1298 (w), 1258 (m), 1243 (w), 1217 (w), 1147 (w), 1122 (m), 1071 (m), 1030 (w), 1008 (w), 964 (w), 875 (w), 822 (w), 789 (w).

(1'*RS*, 4'*SR*, 4a'*SR*, 9'*RS*, 9a'*RS*, 10'*SR*, 11'*RS*)-9',11'-Epoxy-1',3',4',4a',9',9a'-hexahydro-6'-methoxy-10'-methyl-3'-oxo-1',4'-ethanoindeno[2',1'-*c*]pyranyl-acetic acid.



170 **171**

The aldehyde **170** (16 mg, 0.051 mmol), 30% hydrogen peroxide (270 µl, 0.82 mmol) and sodium hydrogenphoshate (2 mg, 0.017 mmol) were dissolved in a 1:1 solution of acetonitrile/water (1 ml) and cooled to 0°C. Sodium chlorite (7.5 mg, 0.082 mmol) in water (100 µl) was added dropwise. The mixture was warmed to room temperature and stirred for 2.5 hours. The reaction was quenched with sodium sulfate (20 mg, 0.168 mmol) and acidified with 6M HCl (1 ml). The mixture was extracted with dichloromethane (4x15 ml) and the combined organic phase was washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate : acetic acid = 1:1:0.02) to afford the acid **171** (11 mg, 65%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.33 (1H, d, $J_{8',7'}$ = 8.2 Hz, H-8'), 6.89 (1H, s, H-5'), 6.87 (1H, d, $J_{7',8'}$ = 8.2 Hz, H-7'), 5.22 (1H, d, $J_{9',9a'}$ = 5.5 Hz, H-9'), 5.12 (1H, dd, $J_{1',9a'}$ = 5.5 Hz, $J_{1',11'}$ = 5.8 Hz, H-1'), 4.30 (1H, d, $J_{4a',9a'}$ = 9.4 Hz, H-4a'), 3.94 (1H, d, $J_{11',1'}$ = 5.6 Hz, H-11'), 3.81 (3H, s, **CH_3**O-C6'), 3.53 (1H, ddd, $J_{9a',4a'}$ = 9.4 Hz, $J_{9a',1'}$ = 5.5, Hz, $J_{9a',9'}$ = 5.5 Hz, H-9a'), 2.96 (1H, d, J_{gem} = 15.9 Hz, H-1α), 2.34 (1H, d, J_{gem} = 16.0 Hz, H-1β), 1.67 (1H, q, $J_{10',Me}$ = 7.2 Hz, H-10'), 0.88 (3H, d, $J_{Me,10'}$ = 7.5 Hz, **CH_3**-C10').

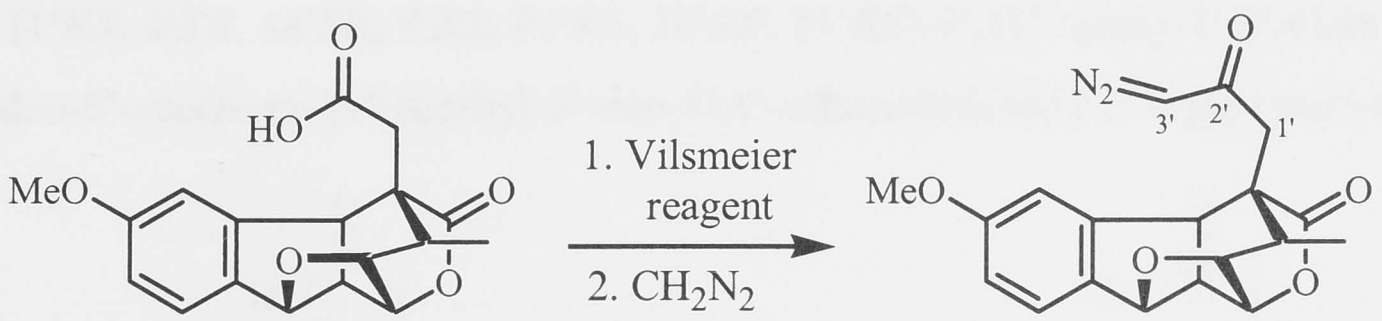
^{13}C-NMR (75MHz, $CDCl_3$): δ 176.74 (C2), 174.83 (C3'), 161.32 (C6'), 142.74 (C4b'), 137.01 (C8a'), 126.41 (C8'), 115.10 (C5'), 111.91 (C7'), 83.20 (C11'), 79.70 (C1'), 79.48 (C9'), 55.78 (**CH_3**O-C6'), 47.76 (C9a'), 46.29 (C4'), 46.01 (C4a'), 40.38 (C10'), 33.98 (C1), 16.11 (**CH_3**-C10').

LRMS (*m/z*): 330 (M^+, 9%), 296 (100), 271 (33), 256 (35), 242 (15), 229 (53), 214 (12), 201 (11), 187 (6), 175 (58), 161 (12), 149 (8), 128 (7), 115 (13), 83 (43), 57 (21).

HRMS (EI): Found 330.1107 (M^+), $C_{18}H_{18}O_6$ requires 330.1103.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3500 (br), 2931 (w), 1755 (s), 1607 (w), 1493 (m), 1465 (w), 1378 (w), 1348 (w), 1260 (m), 1173 (w), 1147 (m), 1120 (m), 1071 (m), 1031 (w), 1000 (w), 961 (w), 873 (w), 791 (w), 752 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-(3′-Diazo-2′-oxopropyl)-9,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-10-methyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



171 **172**

Oxalyl chloride (15.5 µl, 0.18 mmol) was added to the acid **171** (6 mg, 0.0.18 mmol) in dry benzene (1 ml). A drop of DMF was added and stirring was continued for 2 hours. The solvent was removed under reduced pressure. Benzene (1 ml) was added and removed under vacuum. This step was repeated twice. The residue was redissolved in tetrahydrofuran (2 ml), which was then added dropwise to an excess of ethereal diazomethane at 0°C and stirred for 6 hours. The mixture was warmed to room temperature and stirred for a further 16 hours. The solvent was removed and the residue was directly chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the diazoketone **172** (4 mg, 62%) as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.34 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 7.15 (1H, d (br), $J_{5,7}$ = 2.5 Hz, H-5), 6.87 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 5.22 (1H, d, $J_{9,9a}$ = 5.3

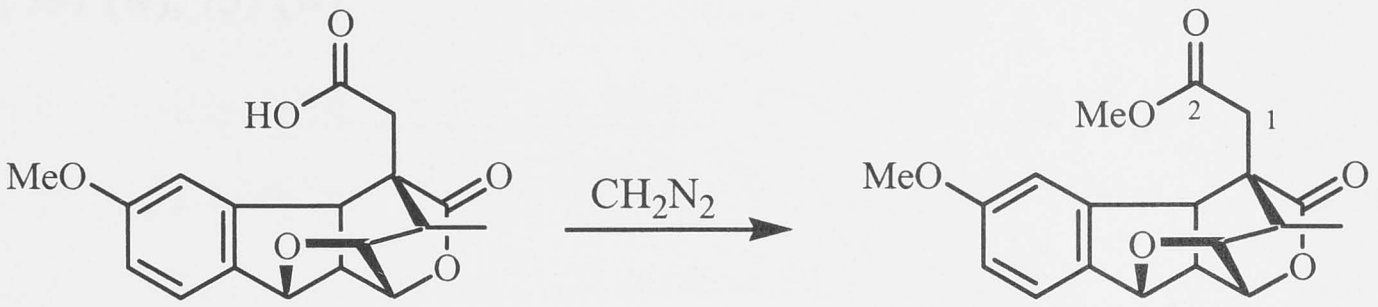
Hz, H-9), 5.10 (1H, dd, $J_{1,9a}$ = 6.2 Hz, $J_{1,11}$ = 5.4 Hz, H-1), 4.90 (1H, s (br) C2'-C**H**N_2), 4.45 (1H, d, $J_{4a,9a}$ = 8.8 Hz, H-4a), 3.93 (1H, d, $J_{11,1}$ = 5.4 Hz, H-11), 3.82 (3H, s, **CH_3**O-C6), 3.51 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 6.1 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.83 (1H, d (br), J_{gem}= 15.5 Hz, H-1'α), 2.25 (1H, d, J_{gem} = 15.5 Hz, H-1'β), 1.68 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.89 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10).

LRMS (*m/z*): 354 (M^+, 3%), 326 (100), 313 (31), 298 (18), 269 (7), 241 (10), 225 (7), 213 (12), 199 (7), 186 (42), 173 (38), 159 (51), 145 (35), 128 (11), 115 (20), 102 (1), 91 (8), 71 (5).

HRMS (EI): Found 354.1214 (M^+), $C_{19}H_{18}N_2O_5$ requires 354.1216.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3099 (w), 2930 (w), 2104 (s), 1753 (s), 1638 (m), 1610 (m), 1491 (m), 1465 (w), 1371 (m), 1346 (w), 1326 (w), 1275 (w), 1258 (w), 1243 (w), 1120 (m), 1069 (m), 1046 (w), 1030 (w), 1000 (w), 999 (w), 822 (w), 790 (w).

Methyl (1'*RS*, 4'*SR*, 4a'*SR*, 9'*RS*, 9a'*RS*, 10'*SR*, 11'*RS*)-9',11'-epoxy-1',3',4',4a',9',9a'-hexahydro-6'-methoxy-10'-methyl-3'-oxo-1',4'-ethanoindeno[2',1'-*c*]pyranyl-acetate.



171 **165**

The acid **171** (15 mg, 0.045 mmol) was dissolved in dichloromethane (500 µl) and added dropwise to an excess of ethereal diazomethane at 0°C. The solution was warmed to room temperature and stirring was continued for 16 hours. The solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the ester **165** (15 mg, 96%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.34 (1H, d, $J_{8',7'}$ = 8.3 Hz, H-8'), 6.86 (1H, dd, $J_{7',8'}$ = 8.3 Hz, $J_{7',5'}$ = 2.2 Hz, H-7'), 5.73 (1H, d, $J_{5',7'}$ = 2.2 Hz, H-5'), 5.21 (1H, d, $J_{9',9a'}$ = 5.4 Hz, H-9'), 5.10 (1H, dd, $J_{1',9a'}$ = 5.5 Hz, $J_{1',11'}$ = 5.6 Hz, H-1'), 4.51 (1H, d, $J_{4a',9a'}$ = 8.9

Hz, H-4a'), 3.92 (1H, d, $J_{11',1'}$ = 5.6 Hz, H-11'), 3.80 (3H, s, **CH$_3$**O-C6'), 3.79 (3H, s, COO**CH$_3$**), 3.52 (1H, ddd, $J_{9a',4a'}$ = 8.8 Hz, $J_{9a',1'}$ = 5.6 Hz, $J_{9a',9'}$ = 5.4 Hz, H-9a'), 2.88 (1H, d, J_{gem} = 16.8 Hz, H-1α), 2.27 (1H, d, J_{gem} = 16.9 Hz, H-1β), 1.66 (1H, q, $J_{10',Me}$ = 7.7 Hz, H-10'), 0.88 (3H, d, $J_{Me,10'}$ = 7.7 Hz, **CH$_3$**-C10').

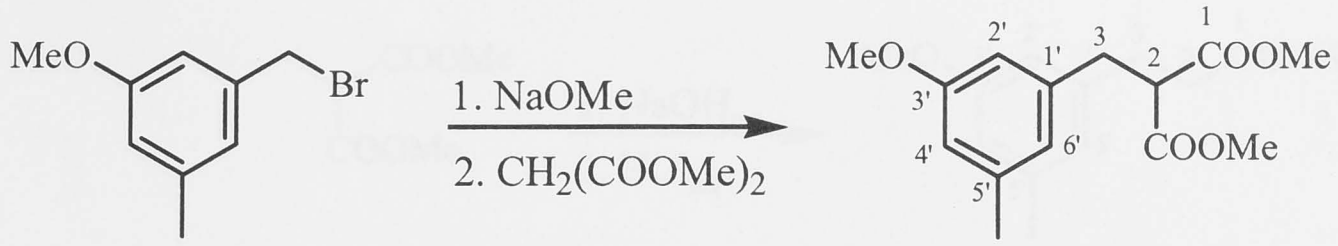
^{13}C-NMR (75MHz, $CDCl_3$): δ 173.16 (C3'), 171.49 (C2), 160.88 (C6'), 143.01 (C4b'), 137.04 (C8a'), 126.22 (C8'), 114.07 (C5'), 111.83 (C7'), 82.92 (C11'), 79.57 (C1'), 79.09 (C9'), 55.43 (**CH$_3$**O-C6'), 51.92 (COO**CH$_3$**), 47.15 (C9a'), 45.79 (C4'), 45.74 (C4a'), 39.99 (C10'), 32.60 (C1), 15.91 (**CH$_3$**-C10').

LRMS (*m/z*): 344 (M^+, 100%), 313 (17), 270 (7), 241 (6), 227 (18), 213 (11), 199 (9), 186 (21), 175 (15), 171 (12), 159 (16), 145 (25), 128 (12), 115 (19), 102 (14), 91 (13), 81 (9), 57 (14).

HRMS (EI): Found 344.1260 (M^+), $C_{19}H_{20}O_6$ requires 344.1260.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2950 (w), 2839 (w), 1756 (s), 1606 (w), 1493 (m), 1465 (w), 1435 (w), 1363 (m), 1347 (w), 1302 (w), 1274 (w), 1261 (m), 1202 (m), 1171 (m), 1147 (w), 1120 (m), 1087 (w), 1072 (m), 1047 (w), 1029 (w), 1002 (m), 963 (w), 875 (w), 823 (w), 791 (w), 757 (w).

Methyl 2-methoxycarbonyl-3-(3'-methoxy-5'-methylbenzene)-propanoate.



187 **188**

To a solution of sodium methoxide, prepared from sodium (2.94 g, 0.128 mol) and absolute methanol (100 ml), was added dimethyl malonate (22.97 g, 0.174 mol) under N_2, followed by addition of the bromide **187** (25 g, 0.116 mol) over 30 minutes. After 16 hours at reflux, most of the methanol was removed under reduced pressure. The remaining residue was diluted with 2M HCl (150 ml) and extracted with ethyl acetate (3x400 ml). The organic phase was combined and washed with water (200 ml), brine (200 ml) and dried over magnesium sulfate. Removal of solvent under reduced pressure, followed by distillation, afforded the malonate **188** (17.9 g, 58%) as a colourless liquid (bp 134°C at 1 mm).

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.59 (1H, s, H-6'), 6.57 (1H, s, H-2'), 6.53 (1H, s, H-4'), 3.75 (3H, s, **CH_3**O-C3'), 3.70 (6H, s, 2x COO**CH_3**), 3.68 (1H, t, $J_{2,3}$ = 7.8 Hz, H-2), 3.15 (2H, d, $J_{3,2}$ = 7.8 Hz, 2x H-3), 2.28 (3H, s, **CH_3**-C5').

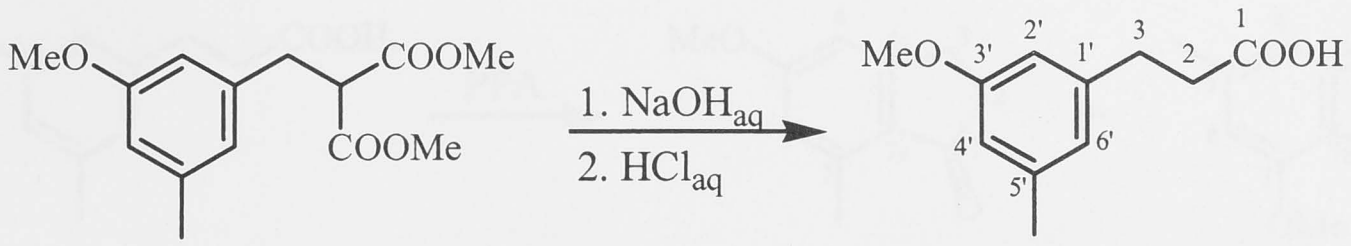
^{13}C-NMR (75MHz, $CDCl_3$): δ 169.50 (2x **C**$OOCH_3$), 159.90 (C3'), 139.81 (C1'), 139.29 (C5'), 122.17 (C6'), 113.30 (C4'), 111.55 (C2'), 55.33 (**CH_3**O-C3'), 53.78 (C2), 52.81 (2x COO**CH_3**), 34.96 (C3), 21.73 (**CH_3**-C5').

LRMS (*m/z*): 266 (M^+, 97%), 235 (11), 206 (100), 191 (12), 175 (92), 165 (25), 148 (25), 135 (54), 117 (13), 105 (17), 91 (31), 79 (15), 77 (22), 59 (21).

HRMS (EI): Found 266.1156 (M^+), $C_{14}H_{18}O_5$ requires 266.1154.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3000 (w), 2953 (w), 2840 (w), 1753 (s), 1737 (s), 1610 (w), 1596 (m), 1462 (w), 1436 (w), 1342 (w), 1290 (w), 1231 (w), 1194 (w), 1153 (m), 1065 (w), 1029 (w), 925 (w), 838 (w), 696 (w).

3-(3'-methoxy-5'-methylphenyl)propanoic acid.



188 **189**

A mixture of the malonate **188** (17.9 g, 0.067 mol), NaOH (10.72 g, 0.268 mol), tetrahydrofuran (80 ml) and water (80 ml) was refluxed for 6 hours. The solution was carefully acidified with concentrated HCl (54 ml) and boiling was continued for a further 24 hours until there was no further evolution of CO_2. After extraction with ethyl acetate (4x400 ml), the organic phase was combined and washed with water (200 ml), brine (200 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C: ethyl acetate = 4:1) to afford the acid **189** (8.75 g, 67%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.62 (1H, s, H-6'), 6.57 (2H, m, H-2', H-4'), 3.78 (3H, s, **CH_3**O-C3'), 2.90 (2H, t, $J_{2,3}$ = 7.7 Hz, 2x H-2), 2.68 (2H, t, $J_{3,2}$ = 7.7 Hz, 2x H-3), 2.30 (3H, s, **CH_3**-C5').

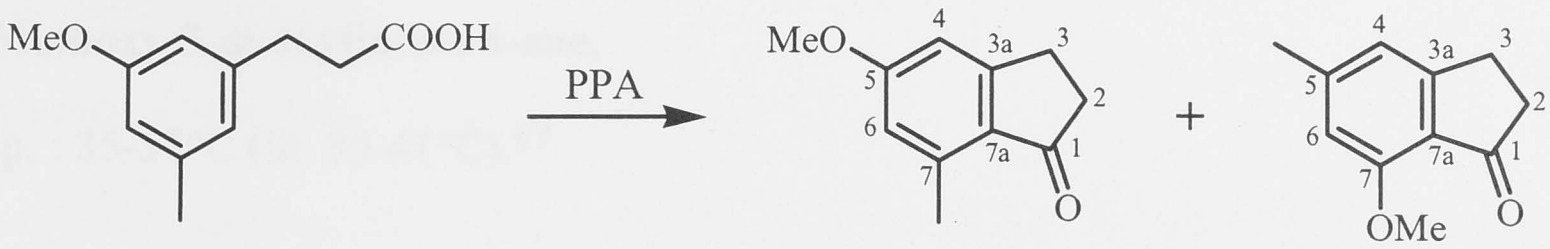
^{13}C-NMR (75MHz, $CDCl_3$): δ 179.64 (**C**OOH), 159.98 (C3'), 141.76 (C1'), 139.84 (C5'), 121.76 (C6'), 112.80 (C4'), 111.24 (C2'), 55.37 (**CH_3**O-C3'), 35.81 (C2), 30.81 (C3), 21.77 (**CH_3**-C5').

LRMS (*m/z*): 194 (M^+, 85%), 149 (100), 135 (56), 119 (10), 105 (11), 91 (25), 77 (14).

HRMS (EI): Found 194.0947 (M^+), $C_{11}H_{14}O_3$ requires 194.0943.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3200 (w), 2937 (w), 1709 (s), 1596 (s), 1463 (w), 1324 (w), 1292 (m), 1193 (w), 1152 (m), 1070 (m), 839 (w), 698 (w), 608 (w).

5-Methoxy-7-methylindan-1-one and 7-Methoxy-5-methylindan-1-one.



189 **190** **191**

The acid **189** (8 g, 0.412 mmol) and polyphosphoric acid (55 g) were stirred at 75°C (oil bath) for 30 minutes, by which time the colour of the reaction mixture had changed to dark-red. The reaction mixture was allowed to cool to room temperature and dissolved with water (10x120 ml). The aqueous suspension was extracted with ethyl acetate (2x600 ml). The combined organic phase was washed with saturated sodium bicarbonate aqueous solution (2x150 ml), brine (100 ml) and dried over magnesium sulfate. After filtration, the mother liquor was concentrated under reduced pressure and chromatographed on silica gel (petroleum ether 40-60°C: ethyl acetate 10:1) to yield the less polar 5-methoxyindanone **190** (4.15 g, 57%) as colourless needles. Further elution afforded the more polar 7-methoxyindanone **191** (871 mg, 12%) as colourless crystals.

5-Methoxy-7-methylindan-1-one.

m.p. : 83-85°C (lit. 83-85°C).[87]

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.69 (1H, d, $J_{6,4}$ = 2.0 Hz, H-6), 6.59 (1H, d, $J_{4,6}$ = 2.0 Hz, H-4), 3.83 (3H, s, **CH_3**O-C5), 2.98 (2H, m, 2x H-3), 2.60 (2H, m, 2x H-2), 2.57 (3H, s, **CH_3**-C7).

^{13}C-NMR (75MHz, $CDCl_3$): δ 206.24 (C1), 164.65 (C5), 159.19 (C3a), 140.91 (C7), 125.38 (C7a), 116.54 (C6), 107.62 (C4), 55.69 (**CH_3**O-C5), 37.23 (C3), 25.75 (C2), 18.70 (**CH_3**-C7).

LRMS (*m/z*): 176 (M^+, 100%), 161 (10), 148 (45), 133 (25), 120 (21), 115 (22), 105 (29), 102 (24), 91 (20), 77 (36), 63 (20).

HRMS (EI): Found 176.0834 (M^+), $C_{11}H_{12}O_2$ requires 176.0837.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3012 (w), 2982 (w), 2958 (w), 1692 (s), 1600 (s), 1453 (m), 1434 (m), 1314 (s), 1278 (m), 1248 (m), 1196 (m), 1149 (s), 1065 (w), 1039 (w), 1013 (w), 871 (m), 850 (m), 701 (w).

Analysis: Calcd for $C_{11}H_{12}O_2$: C, 74.98%; H, 6.83%. Found: C, 74.96%; H, 6.83%.

7-Methoxy-5-methylindan-1-one.

m.p. : 35-37°C (lit. 35-41°C).[87]

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.68 (1H, s, H-6), 6.46 (1H, s, H-4), 3.80 (3H, s, **CH_3**O-C5), 2.87 (2H, m, 2x H-3), 2.50 (2H, m, 2x H-2), 2.28 (3H, s, **CH_3**-C5).

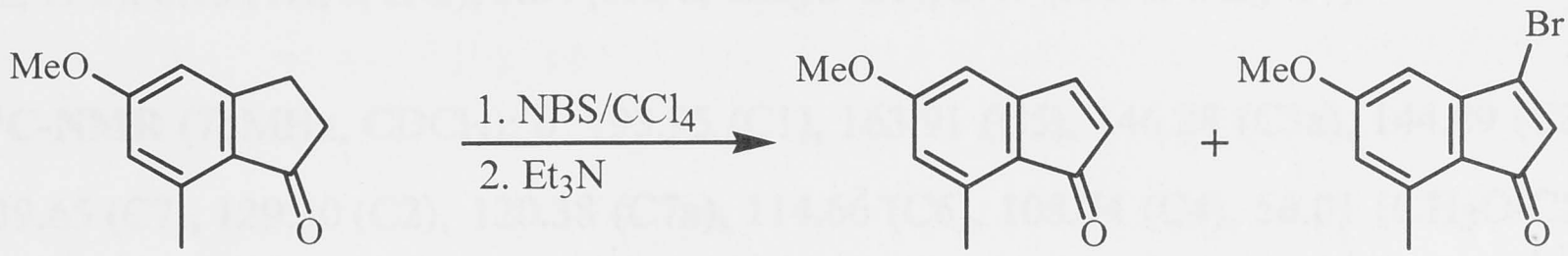
^{13}C-NMR (75MHz, $CDCl_3$): δ 204.41 (C1), 158.40 (C7), 157.98 (C3a), 148.15 (C5), 123.12 (C7a), 119.20 (C4), 110.02 (C6), 55.79 (**CH_3**O-C7), 37.04 (C3), 25.54 (C2), 22.53 (**CH_3**-C5).

LRMS (*m/z*): 176 (M^+, 100%), 161 (27), 147 (99), 133 (22), 129 (19), 117 (43), 115 (35), 105 (25), 91 (24), 77 (24), 63 (13).

HRMS (EI): Found 176.0838 (M^+), $C_{11}H_{12}O_2$ requires 176.0837.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3017 (w), 2977 (w), 2934 (w), 1689 (s), 1586 (s), 1461 (m), 1318 (s), 1282 (w), 1239 (s), 1162 (m), 1084 (s), 1024 (m), 881 (w), 844 (m), 722 (m), 599 (m).

5-Methoxy-7-methyl-1*H*-inden-1-one and 3-Bromo-5-methoxy-7-methyl-1*H*-inden-1-one.



190 **83** **193**

N-Bromosuccinimide (1.2 g, 6.74 mmol) was added to a solution of the indanone **190** (1.2 g, 6.82 mmol) in carbon tetrachloride (100 ml). The resulting suspension was stirred at reflux with irradiation from a tungsten lamp for 1.5 hours. Triethylamine (4 ml) was added and the reaction mixture was stirred at 85°C (oil bath) for a further 2 hours. The mixture was filtered through a short column of silica gel and washed with ethyl acetate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C: ethyl acetate = 30:1) to afford the less polar 3-bromo-5-methoxyindenone **193** (102 mg, 6%). Further elution afforded

the more polar 5-methoxyindenone **83** (750 mg, 63%) as a yellow oil, and starting material (96 mg).

5-Methoxy-7-methyl-1*H*-inden-1-one.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.23 (1H, d, $J_{3,2}$ = 5.9 Hz, H-3), 6.35 (1H, d, $J_{4,6}$ = 2.2 Hz, H-4), 6.25 (1H, d, $J_{6,4}$ = 2.2 Hz, H-6), 5.73 (1H, d, $J_{2,3}$ = 5.9 Hz, H-2), 3.72 (3H, s, **CH_3**O-C5), 2.37 (3H, s, CH_3-C7).

^{13}C-NMR (75MHz, $CDCl_3$): δ 198.27 (C1), 163.91 (C5), 147.88 (C3a), 146.72 (C3), 139.95 (C7), 129.14 (C2), 120.09 (C7a), 113.35 (C6), 109.53 (C4), 55.71 (**CH_3**O-C5), 17.69 (**CH_3**-C7).

LRMS (*m/z*): 174 (M^+, 100%), 159 (13), 146 (20), 131 (29), 120 (14), 115 (26), 103 (29), 102 (24), 87 (12), 77 (29), 63 (20).

HRMS (EI): Found 174.0680 (M^+), $C_{11}H_{10}O_2$ requires 174.0681.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3010 (w), 2941 (w), 2845 (w), 1695 (s), 1618 (s), 1551 (m), 1465 (m), 1371 (m), 1292 (m), 1276 (m), 1195 (m), 1178 (m), 1146 (s), 1025 (w), 864 (w), 822 (w), 707 (w).

3-Bromo-5-methoxy-7-methyl-1*H*-inden-1-one.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.59 (1H, d, $J_{4,6}$ = 2.0 Hz, H-4), 6.43 (1H, d, $J_{6,4}$ = 2.0 Hz, H-6), 6.13 (1H, s, H-2), 3.84 (3H, s, **CH_3**O-C5), 2.47 (3H, s, **CH_3**-C7).

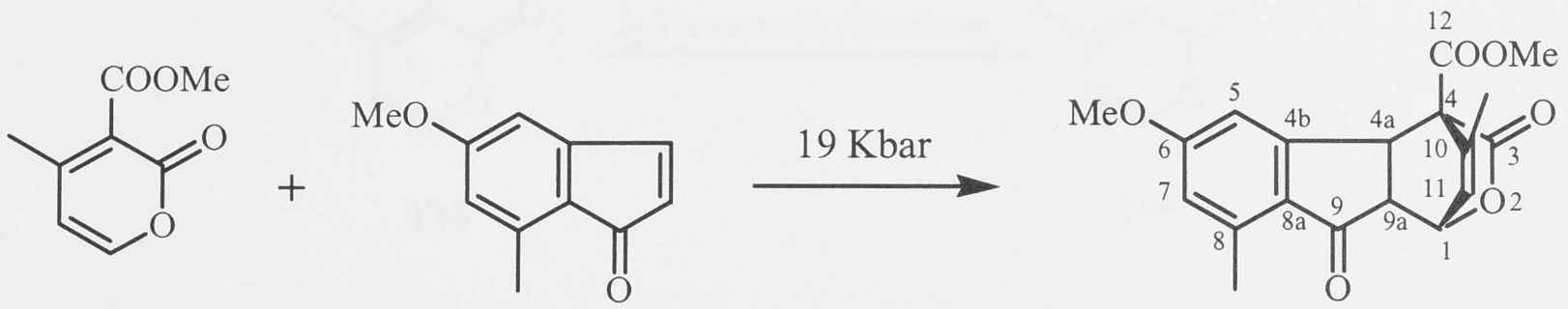
^{13}C-NMR (75MHz, $CDCl_3$): δ 193.95 (C1), 163.91 (C5), 146.28 (C3a), 144.89 (C3), 139.65 (C7), 129.30 (C2), 120.38 (C7a), 114.66 (C6), 108.74 (C4), 56.01 (**CH_3**O-C5), 17.90 (**CH_3**-C7).

LRMS (*m/z*): 254.0 (M^+, ^{80}Br, 53%), 252.0 (M^+, ^{78}Br, 54%), 208 (5), 173 (100), 130 (34), 115 (21), 102 (40), 87 (11), 75 (18), 63 (16).

HRMS (EI): Found 253.9767 (M^+, ^{80}Br), $C_{11}H_9O_2Br$ requires 253.9765; Found 251.9791 (M^+, ^{78}Br), $C_{11}H_9O_2Br$ requires 251.9786.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3010 (w), 2922 (w), 1692 (s), 1596 (m), 1547 (s), 1496 (m), 1372 (m), 1299 (m), 1226 (m), 1170 (m), 1141 (s), 1029 (w), 861 (w), 827 (w), 691 (w).

Methyl (1*SR*, 4*SR*, 4a*SR*, 9a*SR*)-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-3,9-dioxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



136 **83** **194**

The indenone **83** (130 mg, 0.75 mmol) and the pyrone **136** (110 mg, 0.66 mmol) were dissolved in a minimum of dichloromethane (1 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 20 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the cycloadduct **194** (158 mg, 71%, based on pyrone). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p.: 133-135°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.91 (1H, s, H-7), 6.64 (1H, s, H-5), 5.93 (1H, d, $J_{11,1}$ = 5.1 Hz, H-11), 5.36 (1H, dd, $J_{1,9a}$ = 4.5 Hz, $J_{1,11}$ = 5.1 Hz, H-1), 4.30 (1H, d, $J_{4a,9a}$ = 6.9 Hz, H-4a), 3.99 (3H, s, COO**CH$_3$**), 3.80 (3H, s, **CH$_3$**O-C6), 3.45 (1H, dd, $J_{9a,4a}$ = 6.9 Hz, $J_{9a,1}$ = 4.5 Hz, H-9a), 2.51 (3H, s, **CH$_3$**-C8), 1.56 (3H, s, **CH$_3$**-C10).

^{13}C-NMR (75MHz, $CDCl_3$): δ 200.21 (C9), 170.35 (C3), 168.43 (C12), 164.98 (C6), 155.11 (C4b), 141.84 (C10), 140.37 (C8), 130.10 (C8a), 123.83 (C11), 117.77 (C5), 108.61 (C7), 74.43 (C1), 63.46 (C4), 55.86 (**CH$_3$**O-C6), 53.23 (COO**CH$_3$**, C9a), 38.92 (C4a), 20.21 (**CH$_3$**-C10), 18.89 (**CH$_3$**-C8).

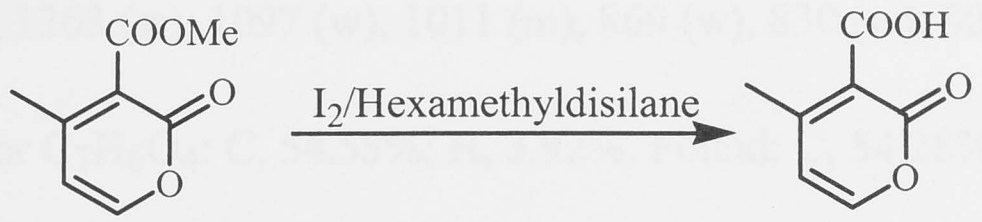
LRMS (*m/z*): 342 (M^+, 13%), 270 (1), 239 (57), 196 (3), 174 (100), 165 (6), 152 (6), 148 (6), 120 (11), 115 (6), 91 (5), 83 (7), 77 (5).

HRMS (EI): Found 343.1173 (M^+ + H), $C_{19}H_{19}O_6$ requires 343.1182.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2956 (w), 1758 (s), 1697 (s), 1597 (s), 1446 (w), 1379 (w), 1359 (w), 1344 (w), 1308 (m), 1276 (m), 1251 (m), 1232 (w), 1192 (w), 1149 (s), 1096 (w), 1079 (m), 1027 (w), 957 (w), 866 (w), 792 (w).

Analysis: Calcd for $C_{19}H_{18}O_6$: C, 66.66%; H, 5.30%. Found: C, 66.17%; H, 4.89%.

4-Methyl-2-oxo-2*H*-pyran-3-carboxylic acid.



136 **195**

A mixture of hexamethyldisilane (2.5 ml, 12.2 mmol) and iodine (1.55 g, 12.2 mmol) was carefully heated to 50°C in a dry 250 ml round-bottomed flask equipped with a reservoir and a long reflux condenser. A violent exothermic reaction occurred, and a homogeneous reddish brown solution resulted, which was heated under reflux for 1.5 hours to form a colourless liquid. The pyrone **136** (2 g, 11.9 mmol) in 50 ml of dry chloroform was added, and the mixture was heated at reflux for 24 hours. The reaction mixture was cooled to 25°C, and 2 ml of water was added. The mixture was stirred for 10 minutes and then diluted with dichloromethane (100 ml). Saturated aqueous sodium thiosulfate (5 ml) was added, and the mixture was stirred until colourless. The organic later was separated and the aqueous layer was extracted with dichloromethane (3x100 ml). The combined organic solution was then washed with saturated aqueous sodium thiosulfate solution (20 ml), dried with magnesium sulfate, filtered and removed under reduced pressure. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate : acetic acid 1:1:0.02) to yield the acid **195** (1.381 g, 75 %). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 116-117°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.61 (1H, d, $J_{6,5}$ = 5.2 Hz, H-5), 6.46 (1H, d, $J_{5,6}$ = 5.1 Hz, H-4), 2.78 (3H, s, **CH_3**-C4).

^{13}C-NMR (75MHz, $CDCl_3$): δ 167.90 (**C**OOH), 166.02 (C2), 163.40 (C4), 152.06 (C6), 114.37 (C5), 112.85 (C3), 23.78 (**CH_3**-C4).

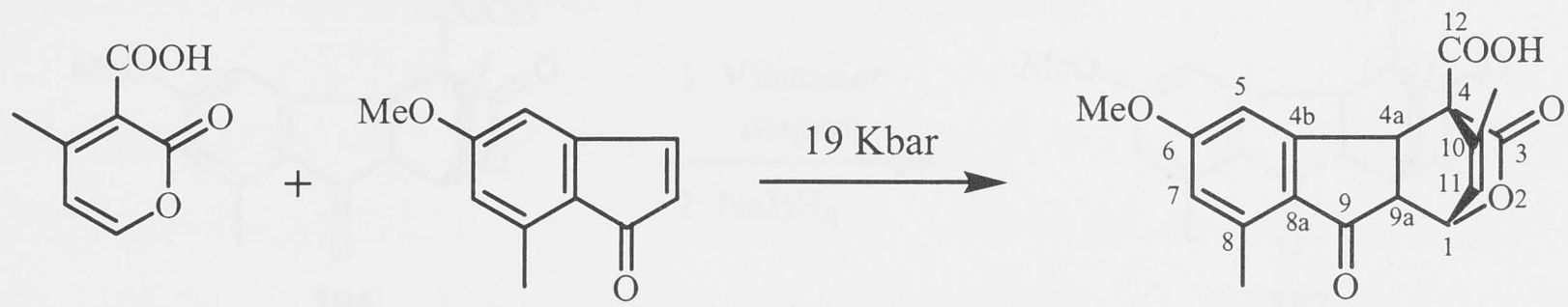
LRMS (*m/z*): 154 (M^+, 54%), 136 (100), 126 (32), 110 (79), 108 (63), 98 (54), 81 (31), 69 (19), 67 (20), 52 (47).

HRMS (EI): Found 154.0263 (M^+), $C_7H_6O_4$ requires 154.0266.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3500 (br), 3074 (w), 2971 (w), 1725 (m), 1658 (m), 1618 (m), 1524 (s), 1374 (s), 1263 (w), 1097 (w), 1011 (m), 869 (w), 830 (w), 805 (m) 621 (w).

Analysis: Calcd for $C_7H_6O_4$: C, 54.55%; H, 3.92%. Found: C, 54.28%; H, 4.00%.

(1*SR*, 4*SR*, 4a*SR*, 9a*SR*)-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-3,9-dioxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylic acid.



195 **83** **196**

The indenone **83** (1.42 g, 9.22 mol) and the pyrone **195** (1.604 g, 9.22 mol) were dissolved in a minimum of dichloromethane (10 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 16 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate : acetic acid = 1:2:0.03) to yield the cycloadduct **196** (2.07 g, 68%, based on pyrone). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 158-160°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.08 (1H, s, H-7), 6.58 (1H, s, H-5), 5.85 (1H, d, $J_{11,1}$ = 4.9 Hz, H-11), 5.30 (1H, dd, $J_{1,9a}$ = 4.7 Hz, $J_{1,11}$ = 4.9 Hz, H-1), 4.24 (1H, d, $J_{4a,9a}$ = 6.7 Hz, H-4a), 3.75 (3H, s, **CH_3**O-C6), 3.38 (1H, dd, $J_{9a,4a}$ = 6.7 Hz, $J_{9a,1}$ = 4.7 Hz, H-9a), 2.45 (3H, s, **CH_3**-C8), 1.56 (3H, s, **CH_3**-C10).

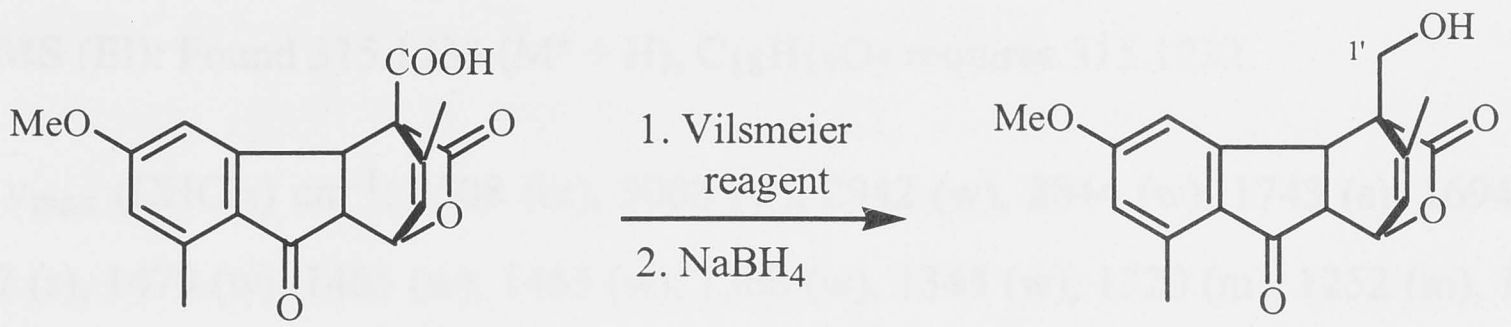
^{13}C-NMR (75MHz, $CDCl_3$): δ 200.63 (C9), 171.47 (C12), 170.11 (C3), 165.01 (C6), 156.78 (C4b), 141.45 (C10), 141.34 (C8), 130.00 (C8a), 123.31 (C11), 117.88 (C5), 108.70 (C7), 74.44 (C1), 63.48 (C4), 55.86 (**CH_3**O-C6), 53.37 (C9a), 38.99 (C4a), 20.29 (**CH_3**-C10), 18.82 (**CH_3**-C8).

LRMS (*m/z*): 328 (M^+, 3%), 239 (100), 225 (26), 196 (7), 174 (28), 165 (11), 148 (28), 120 (27), 84 (37), 78 (31), 66 (46).

HRMS (EI): Found 328.0941 (M^+), $C_{18}H_{16}O_6$ requires 328.0947.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3430 (br), 3003 (w), 2959 (w), 2920 (w), 2845 (w), 1750 (s), 1695 (s), 1596 (s), 1447 (w), 1360 (w), 1345 (m), 1316 (m), 1277 (m), 1251 (m), 1200 (w), 1149 (s), 1098 (w), 1074 (w), 1026 (m), 1008 (m), 948 (w), 869 (w), 778 (w).

(1*SR*, 4*SR*, 4a*SR*, 9a*SR*)-1,4,4a,9a-Tetrahydro-4-hydroxymethyl-6-methoxy-8,10-dimethyl-9-oxo-1,4-ethenoindeno[2,1-*c*]pyran-3(4*H*)-one.



196 **197**

Oxalyl chloride (1.73 ml, 20 mmol) was added to the acid **196** (1.3 g, 4 mmol) in dry tetrahydrofuran (150 ml). DMF (150 µl) was added and stirring was continued for 2 hours. After removal of the solvent, the residue was dissolved in benzene (50 ml) which was subsequently removed under vacuum. This step was repeated twice. The residue was redissolved in tetrahydrofuran (150 ml) and cooled to 0°C. A solution of sodium borohydride (454 mg, 11.9 mmol) in DMF (5 ml) was added over 5 minutes. Stirring was continued for 5 hours at room temperature. The mixture was acidified with 2M HCl (50 ml) and the solvent was removed under reduced pressure. The product was extracted with dichloromethane (3x250 ml) and the combined organic phase was washed with brine (50 ml), dried over magnesium sulfate and filtered. The solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the alcohol **197** (820 mg, 66%) and starting material (86 mg). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 146-148°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.86 (1H, s, H-7), 6.66 (1H, s, H-5), 6.04 (1H, d, $J_{11,1}$ = 4.9 Hz, H-11), 5.41 (1H, dd, $J_{1,9a}$ = 4.9 Hz, $J_{1,11}$ = 4.9 Hz, H-1), 4.45 (1H, d, J_{gem} = 12.2 Hz, H-1'α), 4.19 (1H, d, J_{gem} = 12.2 Hz, H-1'β), 3.87 (1H, d, $J_{4a,9a}$ = 6.6 Hz, H-4a), 3.86 (3H, s, **CH_3**O-C6), 3.48 (1H, dd, $J_{9a,4a}$ = 6.6 Hz, $J_{9a,1}$ = 4.9 Hz, H-9a), 2.52 (3H, s, **CH_3**-C8), 1.38 (3H, s, **CH_3**-C10).

^{13}C-NMR (75MHz, $CDCl_3$): δ 201.11 (C9), 176.02 (C3), 164.89 (C6), 154.85 (C4b), 141.80 (C10), 140.74 (C8), 130.17 (C8a), 124.82 (C11), 117.86 (C5), 108.70 (C7), 74.29 (C1), 59.42 (C1'), 55.98 (**CH_3**O-C6), 55.46 (C4), 53.43 (C9a), 36.42 (C4a), 18.84 (**CH_3**-C8), 16.83 (**CH_3**-C10).

LRMS (*m/z*): 315 (M^+ + H, 2%), 239 (32), 225 (5), 196 (3), 174 (100), 165 (6), 148 (3), 120 (8), 115 (7), 103 (4), 91 (5), 77(7).

HRMS (EI): Found 315.1233 (M^+ + H), $C_{18}H_{19}O_5$ requires 315.1232.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3508 (br), 3008 (w), 2942 (w), 2844 (w), 1743 (s), 1694 (s), 1597 (s), 1479 (w), 1465 (w), 1453 (w), 1360 (w), 1345 (w), 1320 (m), 1252 (m), 1235 (w), 1194 (w), 1150 (s), 1091 (w), 1065 (w), 1048 (w), 1009 (w), 985 (w), 868 (w), 757 (w).

Analysis: Calcd for $C_{18}H_{18}O_5$: C, 68.78%; H, 5.77%. Found: C, 68.54%; H, 6.11%.

(1*SR*, 4*SR*, 4a*SR*, 9a*SR*)-4-(*tert.*-Butyldimethylsilyloxymethyl)-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-9-oxo-1,4-ethenoindeno[2,1-*c*]pyran-3(4*H*)-one.

197 **198**

tert.-Butyldimethylsilyl trifluoromethanesulfonate (272 µl, 1.18 mmol) was added dropwise over 10 minutes to the alcohol **197** (310 mg, 0.99 mmol) and *N,N*-diisopropylethylamine (258 µl, 1.49 mmol) in dichloromethane (30 ml) at 0°C. Stirring was continued at room temperature for 2 hours. The mixture was diluted with dichloromethane (150 ml), washed with 2M HCl (20 ml), brine (20 ml) and dried over magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 6:1) to yield the ether **198** (350 mg, 83%). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 155-157°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.99 (1H, s, H-7), 6.66 (1H, s, H-5), 5.99 (1H, d, $J_{11,1}$ = 5.1 Hz, H-11), 5.36 (1H, dd, $J_{1,9a}$ = 4.9 Hz, $J_{1,11}$ = 5.1 Hz, H-1), 4.49 (1H, d, J_{gem} = 10.5 Hz, H-1'α), 4.12 (1H, d, J_{gem} = 10.5 Hz, H-1'β), 4.01 (1H, d, $J_{4a,9a}$ = 7.0 Hz, H-4a), 3.85 (3H, s, **CH_3**O-C6), 3.48 (1H, dd, $J_{9a,4a}$ = 6.9 Hz, $J_{9a,1}$ = 4.9 Hz, H-9a), 2.53 (3H, s, **CH_3**-C8), 1.32 (3H, s, **CH_3**-C10), 0.97 (9H, s, **$(CH_3)_3$**-C), 0.26 (3H, s, **CH_3**-Si), 0.24 (3H, s, **CH_3**-Si).

^{13}C-NMR (75MHz, $CDCl_3$): δ 201.87 (C9), 173.71 (C3), 164.95 (C6), 155.87 (C4b), 141.46 (C10), 140.75 (C8), 130.39 (C8a), 125.13 (C11), 118.11 (C5), 108.18 (C7), 73.46 (C1), 58.42 (C1'), 55.92 (**CH_3**O-C6), 55.30 (C4), 53.20 (C9a), 35.75 (C4a), 26.15 (**$(CH_3)_3$**-C), 18.81 (**CH_3**-C8), 18.53 ($(CH_3)_3$-**C**), 17.03 (**CH_3**-C10), -5.05 (**CH_3**-Si), -5.23 (**CH_3**-Si).

LRMS (*m/z*): 371 (M^+ - C_4H_9, 6%), 325 (72), 252 (64), 239 (100), 223 (39), 197 (36), 179 (13), 165 (21), 153 (7), 115 (10), 89 (22), 77 (57), 75 (56).

HRMS (EI): Found 371.1319 (M^+ - C_4H_9), $C_{20}H_{23}O_5Si$ requires 371.1315.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2951 (m), 2929 (m), 2855 (w), 1758 (s), 1698 (s), 1598 (s), 1470 (w), 1357 (w), 1344 (w), 1321 (m), 1250 (m), 1232 (w), 1194 (w), 1149 (s), 1097 (w), 1023 (w), 991 (w), 861 (w), 838 (m), 777 (w).

(1*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*)-4-(*tert.*-Butyldimethylsilyloxymethyl)-1,4,4a,9a-tetrahydro-9-hydroxy-6-methoxy-8,10-dimethyl-1,4-ethenoindeno[2,1-*c*]pyran-3(4*H*)-one.

198 **252**

Sodium borohydride (117 mg, 3.08 mmol) was added to the ketone **198** (880 mg, 2.06 mmol) in tetrahydrofuran (50 ml) and methanol (1 ml) and the reaction mixture was stirred at room temperature for 3 hours. Acetone (5 ml) was added to decompose the excess borohydride. The solution was acidified with 2M HCl (30 ml) and extracted with

ethyl acetate (3x100 ml). The organic phase was washed with brine (20 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 4:1) to yield the alcohol **252** (787 mg, 89%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.78 (1H, s, H-7), 6.63 (1H, s, H-5), 6.13 (1H, d, $J_{11,1}$ = 3.2 Hz, H-11), 5.34 – 5.25 (2H, m, H-1, H-9), 4.52 (1H, d, J_{gem} = 10.7 Hz, H-1'α), 4.23 (1H, d, J_{gem} = 10.4 Hz, H-1'β), 3.96 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.77 (3H, s, **CH_3**O-C6), 3.54 (1H, ddd, $J_{9a,4a}$ = 8.7 Hz, $J_{9a,1}$ = 4.2 Hz, $J_{9a,9}$ = 8.5 Hz, H-9a), 2.34 (3H, s, **CH_3**-C8), 1.46 (3H, s, **CH_3**-C10), 0.95 (9H, s, **$(CH_3)_3$**-C), 0.25 (3H, s, **CH_3**-Si), 0.23 (3H, s, **CH_3**-Si).

^{13}C-NMR (75MHz, $CDCl_3$): δ 175.03 (C3), 160.96 (C6), 141.59 (C4b), 140.51 (C10), 137.43 (C8), 136.54 (C8a), 126.35 (C11), 116.79 (C5), 107.20 (C7), 74.20 (C1), 73.63 (C9), 58.64 (C1'), 55.97 (**CH_3**O-C6), 55.61 (C4), 48.67 (C9a), 43.52 (C4a), 26.12 (**$(CH_3)_3$**-C), 18.80 (**CH_3**-C8), 18.51 ($(CH_3)_3$-**C**), 17.42 (**CH_3**-C10), -5.06 (**CH_3**-Si), -5.24 (**CH_3**-Si).

LRMS (*m/z*): 429 (M^+ - H, 1%), 413 (1), 397 (1), 373 (9), 327 (12), 311 (6), 254 (31), 237 (43), 223 (17), 197 (100), 176 (28), 159 (25), 105 (13), 75 (21).

HRMS (EI): Found 429.2092 (M^+ - H), $C_{24}H_{33}O_5Si$ requires 429.2097.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3543 (br), 2951 (m), 2929 (m), 2855 (w), 1750 (s), 1731 (s), 1654 (w), 1606 (m), 1481 (m), 1470 (m), 1442 (w), 1377 (w), 1362 (w), 1335 (w), 1277 (m), 1255 (m), 1142 (s), 1100 (s), 1058 (w), 1021 (w), 980 (w), 945 (w), 839 (m), 778 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-4-(*tert.*-Butyldimethylsilyloxymethyl)-1,4,4a,9a-tetrahydro-9,11-dihydroxy-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.

252 **199**

2M Borane-dimethyl sulfide in tetrahydrofuran (1.02 ml, 2.04 mmol) was added dropwise over 30 minutes to the alkene **252** (350 mg, 0.814 mmol) in dichloromethane (25 ml) at 0°C. Stirring was continued at room temperature for 5 hours. Triethylamine *N*-oxide (700 mg, 6.3 mmol) was added and the mixture was heated under reflux for 16 hours. The solution was filtered through a short pad of silica gel and the solvent was removed under reduced vacuum. The residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 1:1) to afford the alcohol **199** (140 mg, 38%) as a colourless oil and starting material (42 mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.64 (1H, s, H-7), 6.62 (1H, s, H-5), 5.46 (1H, d, $J_{9,9a}$ = 9.6 Hz, H-9), 4.90 (1H, d, $J_{1,9a}$ = 4.0 Hz, H-1), 4.35 (1H, d, J_{gem} = 5.2 Hz, H-1'α), 4.11 (1H, d, $J_{11,10}$ = 3.2 Hz, H-11), 3.96 (1H, d, J_{gem} = 5.2 Hz, H-1'β), 3.73 (3H, s, **CH_3**O-C6), 3.54 (1H, d, $J_{4a,9a}$ = 10.4 Hz, H-4a), 3.21 (1H, ddd, $J_{9a,4a}$ = 10.3 Hz, $J_{9a,1}$ = 4.0 Hz, $J_{9a,9}$ = 9.7 Hz, H-9a), 2.34 (3H, s, **CH_3**-C8), 1.66 (1H, dq, $J_{10,Me}$ = 7.3 Hz, $J_{10,11}$ = 3.2 Hz, H-10), 0.86 (9H, s, **$(CH_3)_3$**-C), 0.61 (3H, d, $J_{Me,10}$ = 7.3 Hz, **CH_3**-C10), 0.15 (3H, s, **CH_3**-Si), 0.13 (3H, s, **CH_3**-Si).

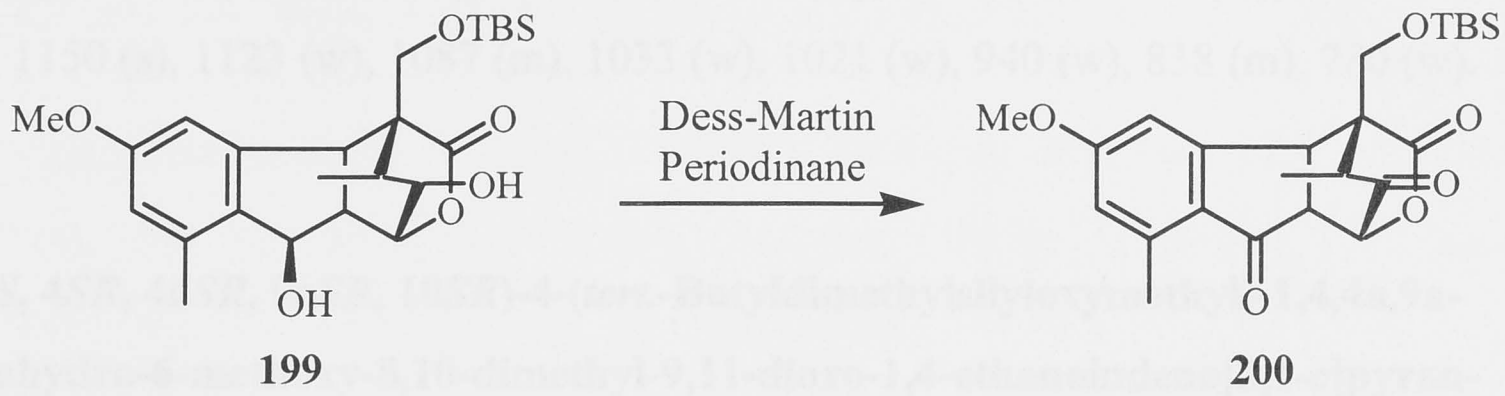
^{13}C-NMR (75MHz, $CDCl_3$): δ 177.15 (C3), 160.56 (C6), 142.53 (C4b), 138.47 (C8), 134.92 (C8a), 116.57 (C5), 108.33 (C7), 81.90 (C11), 74.42 (C9), 72.79 (C1), 60.11 (C1'), 55.56 (**CH_3**O-C6), 51.35 (C4), 44.71 (C9a), 40.60 (C4a), 39.89 (C10), 26.06 ((**CH_3**)$_3$-C), 18.95 (**CH_3**-C8), 18.48 ((CH_3)$_3$-**C**), 14.19 (**CH_3**-C10), -5.19 (**CH_3**-Si), -5.27 (**CH_3**-Si).

LRMS (*m/z*): 449 (M^+ + H, 1%), 432 (2), 420 (2), 414 (2), 391 (57), 373 (11), 329 (9), 311 (10), 271 (6), 254 (40), 237 (58), 225 (25), 214 (17), 199 (53), 189 (26), 171 (76), 160 (49), 135 (10), 107 (23), 85 (53), 75 (100), 66 (57).

HRMS (EI): Found 449.2371 ($M^+ + H$), $C_{24}H_{37}O_6Si$ requires 449.2359.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3400 (br), 2929 (m), 2855 (w), 1752 (s), 1605 (m), 1482 (w), 1378 (w), 1255 (m), 1142 (s), 1104 (s), 1044 (m), 838 (m), 778 (w).

(1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*RS*)-4-(*tert.*-Butyldimethylsilyloxymethyl)-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-9,11-dioxo-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



199 **200**

The diol **199** (316 mg, 0.705 mmol) in tetrahydrofuran (5 ml) was added dropwise over 10 minutes to the Dess Martin periodinane (1.35 g, 2.82 mmol) in tetrahydrofuran (30 ml). The solution was stirred for 16 hours at room temperature. A 1:1 mixture of saturated aqueous sodium thiosulfate and sodium bicarbonate (5 ml) was added and stirring was continued for 1 hour. The product was extracted with ethyl acetate (3x100 ml) and the combined organic phase was washed with saturated sodium thiosulfate (20 ml) and brine (20 ml). After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 5:1) to afford the diketone **200** (182 mg, 58%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.91 (1H, s, H-7), 6.74 (1H, s, H-5), 5.04 (1H, d, $J_{1,9a}$ = 5.6 Hz, H-1), 4.25 (1H, d, J_{gem} = 10.3 Hz, H-1'α), 4.11 (1H, d, J_{gem} = 10.4 Hz, H-1'β), 4.03 (1H, d, $J_{4a,9a}$ = 8.7 Hz, H-4a), 3.87 (3H, s, **CH_3**O-C6), 3.66 (1H, dd, $J_{9a,4a}$ = 8.7 Hz, $J_{9a,1}$ = 5.7 Hz, H-9a), 2.57 (3H, s, **CH_3**-C8), 2.53 (1H, q, $J_{10,Me}$ = 7.4 Hz, H-10), 0.96 (9H, s, **$(CH_3)_3$**-C), 0.45 (3H, d, $J_{Me,10}$ = 7.4 Hz, **CH_3**-C10), 0.24 (3H, s, **CH_3**-Si), 0.23 (3H, s, **CH_3**-Si).

^{13}C-NMR (75MHz, $CDCl_3$): δ 204.53 (C11), 197.98 (C9), 172.75 (C3), 165.40 (C6), 155.54 (C4b), 142.84 (C8), 128.71 (C8a), 118.26 (C5), 109.00 (C7), 80.74 (C1), 59.38 (C1'), 55.85 (**CH_3**O-C6), 52.43 (C4), 52.06 (C9a), 43.13 (C10), 36.54 (C4a), 25.89

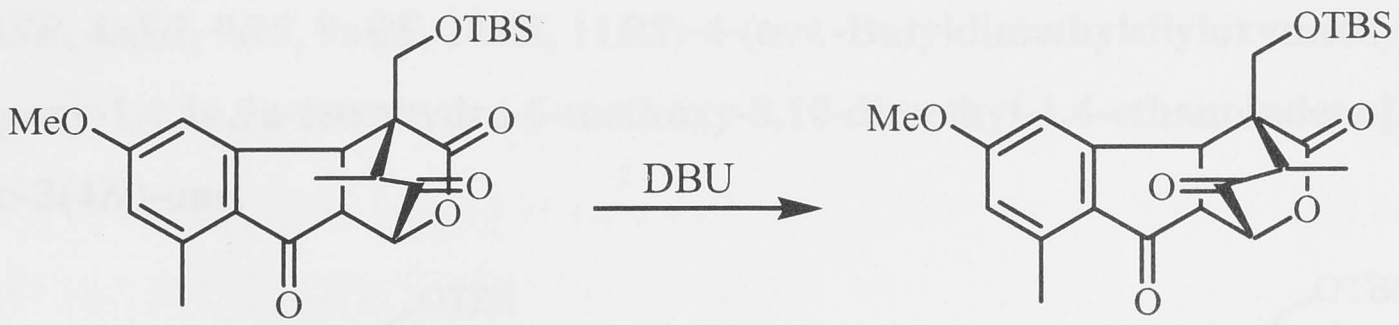
(($\mathbf{CH_3}$)$_3$-C), 18.76 ($\mathbf{CH_3}$-C8), 18.35 ((CH$_3$)$_3$-**C**), 9.65 ($\mathbf{CH_3}$-C10), -5.35 ($\mathbf{CH_3}$-Si), -5.42 ($\mathbf{CH_3}$-Si).

LRMS (*m/z*): 387 (M^+ - C_4H_9, 73%), 369 (1), 343 (3), 295 (3), 267 (5), 239 (3), 213 (3), 199 (20), 187 (100), 171 (7), 159 (36), 129 (5), 116 (6), 75 (22).

HRMS (EI): Found 387.1260 (M^+ - C_4H_9), $C_{20}H_{23}O_6Si$ requires 387.1264.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2951 (w), 2929 (w), 2884 (w), 2855 (w), 1775 (s), 1748 (s), 1700 (s), 1598 (s), 1581 (m), 1462 (w), 1347 (w), 1316 (w), 1250 (w), 1229 (w), 1192 (w), 1150 (s), 1123 (w), 1087 (m), 1033 (w), 1021 (w), 940 (w), 838 (m), 780 (w).

(1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*SR*)-4-(*tert.*-Butyldimethylsilyloxymethyl)-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-9,11-dioxo-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



200 **201**

DBU (2 µl, 0.013) was added to a solution of diketone **200** (182 mg, 0.41 mmol) in tetrahydrofuran (10 ml) and stirred for 1.5 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 5:1) to afford the epimer **201** (179 mg, 98%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.99 (1H, s, H-7), 6.74 (1H, s, H-5), 4.93 (1H, d, $J_{1,9a}$ = 5.4 Hz, H-1), 4.36 (1H, d, J_{gem} = 10.8 Hz, H-1'α), 4.25 (1H, d, J_{gem} = 10.8 Hz, H-1'β), 3.86 (3H, s, $\mathbf{CH_3}$O-C6), 3.65 (1H, d, $J_{4a,9a}$ = 8.8 Hz, H-4a), 3.63 (1H, dd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.4 Hz, H-9a), 2.55 (3H, s, $\mathbf{CH_3}$-C8), 1.83 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.98 (3H, d, $J_{Me,10}$ = 7.6 Hz, $\mathbf{CH_3}$-C10), 0.97 (9H, s, ($\mathbf{CH_3}$)$_3$-C), 0.25 (6H, s, ($\mathbf{CH_3}$)$_2$-Si).

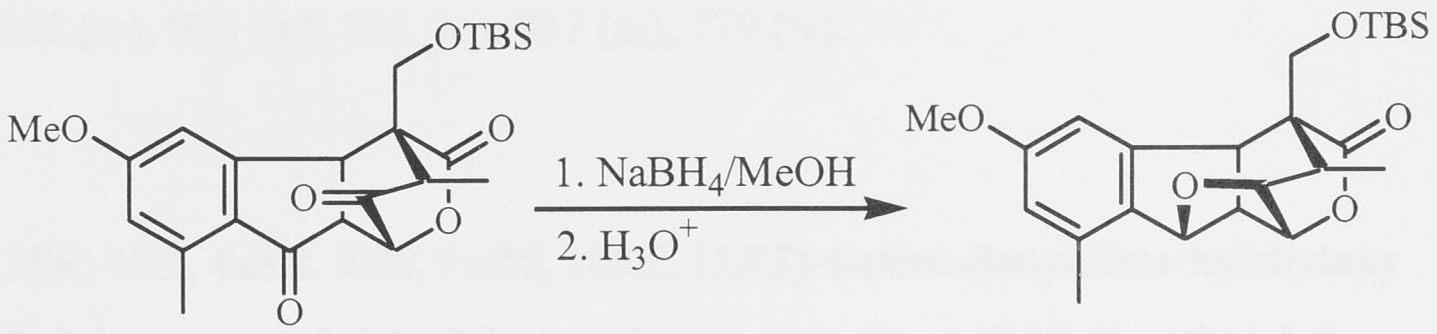
^{13}C-NMR (75MHz, $CDCl_3$): δ 203.74 (C11), 198.68 (C9), 172.32 (C3), 165.89 (C6), 154.66 (C4b), 142.66 (C8), 129.19 (C8a), 118.57 (C5), 109.08 (C7), 81.03 (C1), 60.25 (C1'), 56.01 (**CH_3**O-C6), 52.19 (C4), 50.51 (C9a), 41.98 (C10), 37.50 (C4a), 26.10 ((**CH_3**)$_3$-C), 18.93 (**CH_3**-C8), 18.48 ((CH$_3$)$_3$-**C**), 11.78 (**CH_3**-C10), -5.07 (**CH_3**-Si), -5.23 (**CH_3**-Si).

LRMS (*m/z*): 387 (M^+ - C_4H_9, 84%), 369 (1), 343 (4), 295 (3), 267 (5), 239 (3), 213 (4), 199 (17), 187 (100), 171 (5), 159 (30), 129 (3), 116 (5), 75 (17).

HRMS (EI): Found 387.1263 (M^+ - C_4H_9), $C_{20}H_{23}O_6Si$ requires 387.1264.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2951 (w), 2929 (w), 2884 (w), 2855 (w), 1772 (s), 1748 (s), 1700 (s), 1598 (s), 1581 (m), 1462 (w), 1348 (w), 1306 (w), 1250 (w), 1150 (s), 1123 (w), 1087 (m), 1033 (w), 1018 (w), 940 (w), 838 (m), 781 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-(*tert.*-Butyldimethylsilyloxymethyl) -9,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



201 **202**

Sodium borohydride (51 mg, 1.35 mmol) was added to the diketone **201** (260 mg, 0.585 mmol) in tetrahydrofuran (20 ml) and methanol (1 ml). The mixture was stirred at 3 hours at room temperature. Acetone (2 ml) was added and stirred for 10 minutes. The solution was acidified with 2M HCl to pH2 and extracted with ethyl acetate (3x100 ml). The combined organic phase was washed with brine (30 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 5:1) to afford the ether **202** (160 mg, 64%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.89 (1H, s, H-7), 6.66 (1H, s, H-5), 5.30 (1H, d, $J_{9,9a}$ = 5.5 Hz, H-9), 5.06 (1H, dd, $J_{1,9a}$ = 5.5 Hz, $J_{1,11}$ = 5.4 Hz, H-1), 4.13 (1H, d, J_{gem} =

10.3 Hz, H-1'α), 3.90 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.84 (1H, d, $J_{11,1}$ = 5.3 Hz, H-11), 3.76 (3H, s, **CH$_3$**O-C6), 3.45 (1H, ddd, $J_{9a,4a}$ = 9.0 Hz, $J_{9a,1}$ = 5.5 Hz, $J_{9a,9}$ = 5.5 Hz, H-9a), 3.32 (1H, d, J_{gem} = 10.3 Hz, H-1'β), 2.35 (3H, s, **CH$_3$**-C8), 1.63 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.96 (9H, s, **(CH$_3$)$_3$**-C), 0.78 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH$_3$**-C10), 0.21 (3H, s, **CH$_3$**-Si), 0.19 (3H, s, **CH$_3$**-Si).

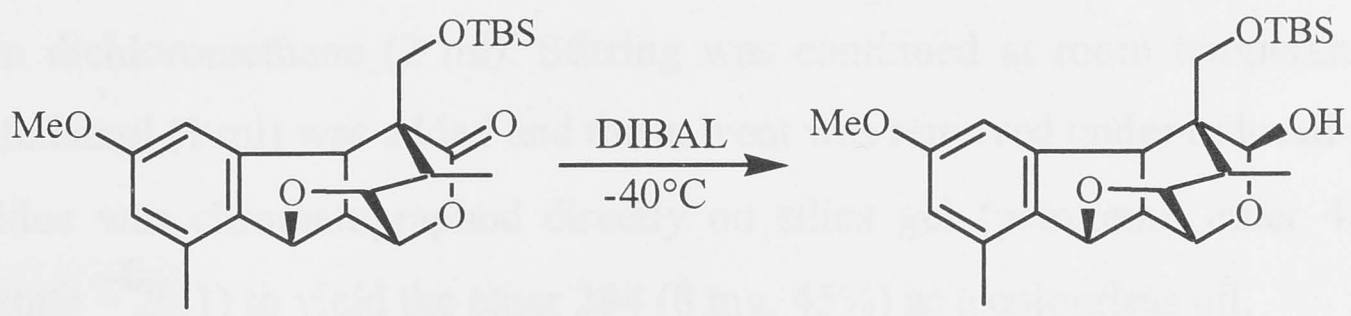
^{13}C-NMR (75MHz, $CDCl_3$): δ 173.32 (C3), 161.39 (C6), 143.14 (C4b), 136.22 (C8), 135.99 (C8a), 116.39 (C5), 108.61 (C7), 81.85 (C11), 80.34 (C1), 79.15 (C9), 60.82 (C1'), 55.68 (**CH$_3$**O-C6), 49.96 (C4), 45.27 (C9a), 45.19 (C4a), 38.11 (C10), 26.15 (**(CH$_3$)$_3$**-C), 18.79 (**CH$_3$**-C8), 18.50 ((CH$_3$)$_3$-**C**), 15.78 (**CH$_3$**-C10), -5.16 (**CH$_3$**-Si), -5.19 (**CH$_3$**-Si).

LRMS (*m/z*): 415 (M^+ - CH_3, 1%), 373 (100), 343 (1), 315 (4), 286 (2), 253 (2), 225 (6), 213 (3), 197 (4), 171 (11), 159 (15), 141 (4), 129 (5), 75 (27).

HRMS (EI): Found 415.1943 (M^+ - CH_3), $C_{23}H_{31}O_5Si$ requires 415.1941.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2951 (m), 2855 (w), 1764 (s), 1608 (m), 1463 (w), 1373 (w), 1349 (w), 1315 (w), 1277 (w), 1254 (m), 1191 (w), 1168 (w), 1138 (m), 1102 (s), 1071 (w), 1041 (w), 996 (w), 896 (m), 837 (m), 779 (w).

(1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-(*tert.*-Butyldimethylsilyloxy methyl)-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3-ol.



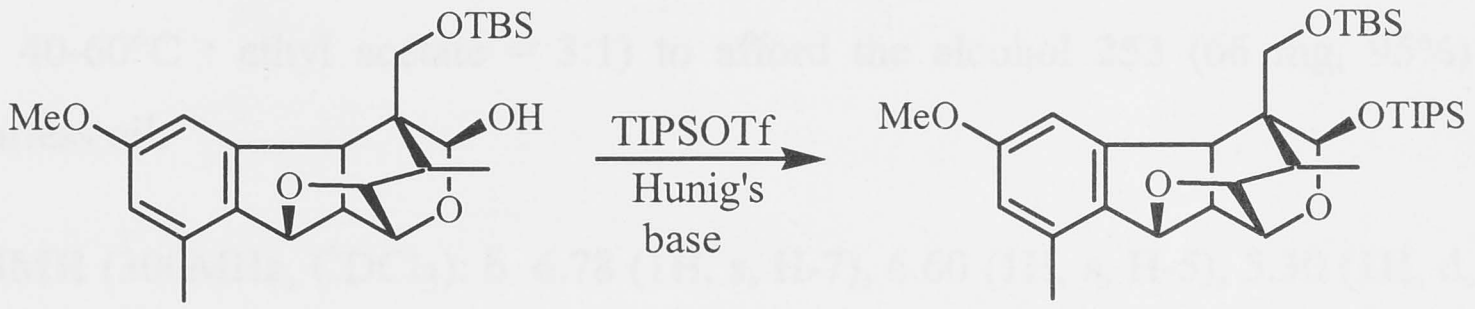
202 **203**

1M Diisobutylaluminum hydride in heptane (56 µl, 0.056 mmol) was added dropwise to the lactone **202** (12 mg, 0.028 mmol) in toluene (1 ml) at –40°C and stirred for 30 minutes. Methanol (100 µl) was added to quench the reaction, followed by 10% HCl (200 µl) at –20°C. The mixture was warmed to room temperature and diluted with ethyl acetate (5 ml). The product was extracted with ethyl acetate (3x5 ml) and the combined

organic phase was washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 4:1) to afford the hemi-acetal **203** (8 mg, 66%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.61 (2H, s, H-7, H-5), 5.30 (1H, s, H-3), 5.28 (1H, d, $J_{9,9a}$ = 5.2 Hz, H-9), 4.56 (1H, dd, $J_{1,9a}$ = 5.8 Hz, $J_{1,11}$ = 5.4 Hz, H-1), 4.05 (1H, d, J_{gem} = 10.2 Hz, H-1'α), 3.91 (1H, d, $J_{4a,9a}$ = 9.1 Hz, H-4a), 3.77 (3H, s, **CH_3**O-C6), 3.71 (1H, d, $J_{11,1}$ = 5.6 Hz, H-11), 3.37 (1H, d, J_{gem} = 10.2 Hz, H-1'β), 3.26 (1H, ddd, $J_{9a,4a}$ = 9.1 Hz, $J_{9a,1}$ = 5.8 Hz, $J_{9a,9}$ = 5.2 Hz, H-9a), 2.36 (3H, s, **CH_3**-C8), 1.34 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.97 (9H, s, **$(CH_3)_3$**-C), 0.87 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10), 0.20 (3H, s, **CH_3**-Si), 0.17 (3H, s, **CH_3**-Si).

(1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-(*tert.*-Butyldimethylsilyloxy methyl)-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-3-triisopropylsilyloxy-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran.



203 **204**

Triisopropylsilyl trifluoromethanesulfonate (64 µl, 0.24 mmol) was added dropwise to the hemi-acetal **203** (13 mg, 0.03 mmol) and *N,N*-diisopropylethylamine (63 µl, 0.36 mmol) in dichloromethane (2 ml). Stirring was continued at room temperature for 6 hours. Methanol (1 ml) was added and the solvent was removed under reduced pressure. The residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 20:1) to yield the ether **204** (8 mg, 45%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.58 (1H, s, H-5), 6.48 (1H, s, H-7), 5.30 (1H, s, H-3), 5.21 (1H, d, $J_{9,9a}$ = 5.1 Hz, H-9), 4.48 (1H, dd, $J_{1,9a}$ = 5.7 Hz, $J_{1,11}$ = 5.4 Hz, H-1), 4.01 (1H, d, J_{gem} = 10.2 Hz, H-1'α), 3.91 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.77 (3H, s, **CH_3**O-C6), 3.73 (1H, d, $J_{11,1}$ = 5.4 Hz, H-11), 3.33 (1H, d, J_{gem} = 10.2 Hz, H-1'β), 3.16 (1H, ddd, $J_{9a,4a}$ = 9.1 Hz, $J_{9a,1}$ = 5.8 Hz, $J_{9a,9}$ = 5.2 Hz, H-9a), 2.35 (3H, s, **CH_3**-

C8), 1.38 (1H, q, $J_{10,Me}$ = 7.5 Hz, H-10), 1.07-1.03 (21H, m, **C$_9$H$_{21}$**-Si) 0.96 (9H, s, **(CH$_3$)$_3$**-C), 0.87 (3H, d, $J_{Me,10}$ = 7.5 Hz, **CH$_3$**-C10), 0.18 (3H, s, **CH$_3$**-Si), 0.16 (3H, s, **CH$_3$**-Si).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,4,4a,9a-tetrahydro-4-hydroxymethyl-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.

202 **253**

1M Tetrabutylammonium fluoride in tetrahydrofuran (331 µl, 0.331 mmol) was added to the ether **202** (95 mg, 0.221 mmol) in tetrahydrofuran (10 ml) and stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml), washed with 2M HCl (10 ml), brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the alcohol **253** (66 mg, 95%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.78 (1H, s, H-7), 6.60 (1H, s, H-5), 5.30 (1H, d, $J_{9,9a}$ = 5.5 Hz, H-9), 5.10 (1H, dd, $J_{1,9a}$ = 5.6 Hz, $J_{1,11}$ = 5.5 Hz, H-1), 4.13 (1H, d, J_{gem} = 9.6 Hz, H-1'α), 3.90 – 3.80 (2H, m, H-4a, H-11), 3.79 (3H, s, **CH$_3$**O-C6), 3.49 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.6 Hz, $J_{9a,9}$ = 5.5 Hz, H-9a), 3.39 (1H, d, J_{gem} = 9.6 Hz, H-1'β), 2.35 (3H, s, **CH$_3$**-C8), 1.61 (1H, q, $J_{10,Me}$ = 7.5 Hz, H-10), 0.83 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH$_3$**-C10).

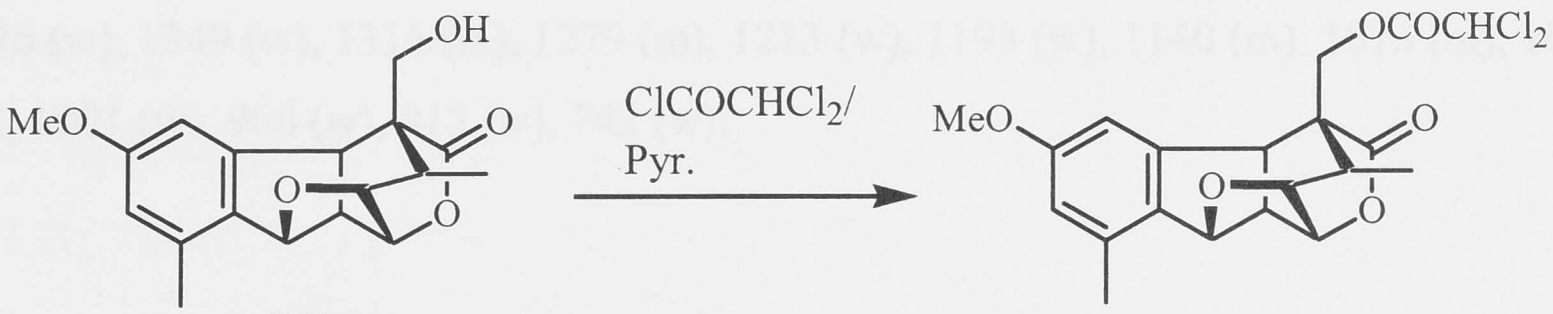
^{13}C-NMR (75MHz, $CDCl_3$): δ 175.81 (C3), 161.42 (C6), 142.48 (C4b), 136.75 (C8), 135.75 (C8a), 116.17 (C5), 108.99 (C7), 81.75 (C11), 80.13 (C1), 79.68 (C9), 60.46 (C1'), 55.70 (**CH$_3$**O-C6), 50.21 (C4), 45.60 (C9a), 45.32 (C4a), 37.51 (C10), 18.80 (**CH$_3$**-C8), 16.22 (**CH$_3$**-C10).

LRMS (*m/z*): 316 (M^+ , 100%), 298 (4), 285 (2), 269 (6), 241 (9), 230 (5), 213 (10), 200 (40), 189 (56), 173 (62), 160 (48), 141 (9), 128 (14), 115 (21), 99 (20), 77 (5), 65 (2).

HRMS (EI): Found 316.1315 (M^+), $C_{18}H_{20}O_5$ requires 316.1311.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3480 (br), 2941 (w), 1751 (s), 1606 (m), 1482 (w), 1376 (w), 1348 (w), 1316 (w), 1277 (w), 1217 (w), 1192 (w), 1138 (s), 1114 (w), 1076 (m), 1026 (w), 997 (w), 959 (w), 893 (m), 869 (w), 743 (w).

(1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-Dichloroacetoxymethyl-9,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3(4*H*)-one.



253 **205**

Dichloroacetyl chloride (25.5 µl, 0.266 mmol) was added to the alcohol **253** (70 mg, 0.222 mmol) and pyridine (25 µl, 0.310 mmol) in dichloromethane (5 ml) and stirred for 1 hour at room temperature. The mixture was acidified with 2M HCl (5 ml) and extracted with dichloromethane (3x25 ml). The combined organic phase was washed with brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the acetate **205** (91 mg, 96%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.67 (1H, s, H-7), 6.52 (1H, s, H-5), 6.09 (1H, s, COC**H**Cl_2), 5.32 (1H, d, $J_{9,9a}$ = 5.4 Hz, H-9), 5.11 (1H, dd, $J_{1,9a}$ = 5.6 Hz, $J_{1,11}$ = 5.4 Hz, H-1), 4.87 (1H, d, J_{gem} = 11.4 Hz, H-1'α), 3.93 – 3.80 (3H, m, H-4a, H-11, H-1'β), 3.73 (3H, s, **CH_3**O-C6), 3.54 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.7 Hz, $J_{9a,9}$ = 5.6 Hz, H-9a), 2.36 (3H, s, **CH_3**-C8), 1.76 (1H, q, $J_{10,Me}$ = 7.7 Hz, H-10), 0.88 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10).

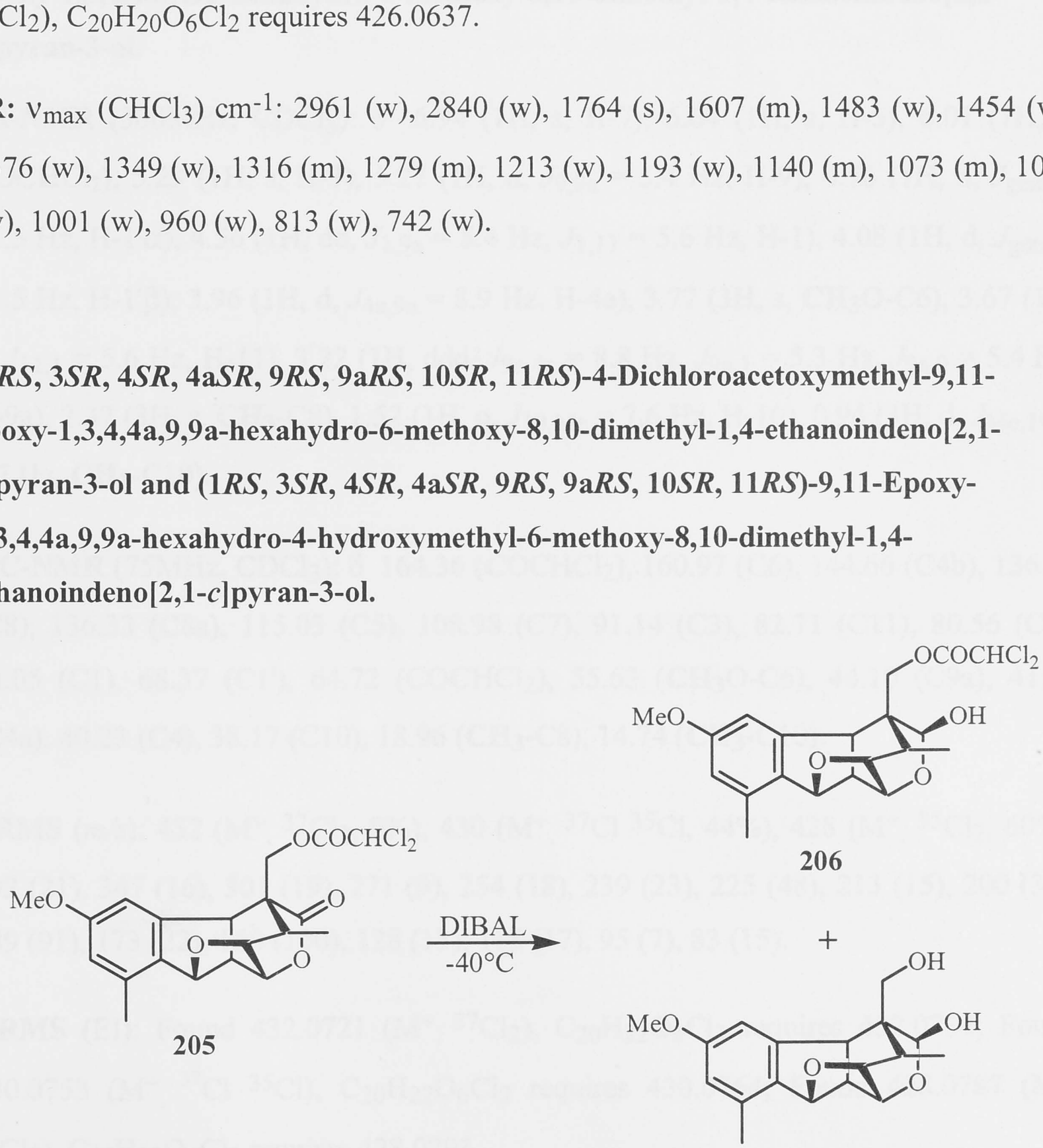
^{13}C-NMR (75MHz, $CDCl_3$): δ 172.09 (C3), 163.95 (**C**O$CHCl_2$), 161.54 (C6), 141.54 (C4b), 137.00 (C8), 135.89 (C8a), 116.58 (C5), 108.03 (C7), 81.77 (C11), 79.89 (C1), 79.33 (C9), 64.63 (CO**C**HCl_2), 64.49 (C1'), 55.70 (**CH_3**O-C6), 48.15 (C4), 45.63 (C9a), 45.33 (C4a), 38.02 (C10), 18.86 (**CH_3**-C8), 16.05 (**CH_3**-C10).

LRMS (*m/z*): 430 (M^+, $^{37}Cl_2$, 16%), 428 (M^+, ^{37}Cl ^{35}Cl, 71%), 426 (M^+, $^{35}Cl_2$, 100%), 392 (7), 299 (14), 269 (6), 241 (11), 213 (9), 200 (25), 189 (10), 173 (14), 159 (23), 115 (7), 81 (5).

HRMS (EI): Found 430.0588 (M^+, $^{37}Cl_2$), $C_{20}H_{20}O_6Cl_2$ requires 430.0578; Found 428.0608 (M^+, ^{37}Cl ^{35}Cl), $C_{20}H_{20}O_6Cl_2$ requires 428.0607; Found 426.0633 (M^+, $^{35}Cl_2$), $C_{20}H_{20}O_6Cl_2$ requires 426.0637.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2961 (w), 2840 (w), 1764 (s), 1607 (m), 1483 (w), 1454 (w), 1376 (w), 1349 (w), 1316 (m), 1279 (m), 1213 (w), 1193 (w), 1140 (m), 1073 (m), 1049 (w), 1001 (w), 960 (w), 813 (w), 742 (w).

(1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-Dichloroacetoxymethyl-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3-ol and (1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,3,4,4a,9,9a-hexahydro-4-hydroxymethyl-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3-ol.



1M Diisobutylaluminum hydride in heptane (351 µl, 0.351 mmol) was added dropwise to the lactone **205** (100 mg, 0.234 mmol) in toluene (5 ml) at –40°C and stirred for 20 minutes. Methanol (200 µl) was added to quench the reaction, followed by 10% HCl (1 ml) also at –40°C. The mixture was warmed to room temperature and diluted with ethyl acetate (10 ml). The product was extracted with ethyl acetate (3x25 ml) and the combined organic phase was washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the hemi-acetal **206** (57 mg, 57%) and the diol **207** (18 mg, 18%), both as colourless oils.

(1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-Dichloroacetoxymethyl-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3-ol.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.94 (1H, s, H-7), 6.64 (1H, s, H-5), 6.01 (1H, s, COC**H**Cl_2), 5.29 (1H, s, H-3), 5.27 (1H, d, $J_{9,9a}$ = 5.4 Hz, H-9), 4.76 (1H, d, J_{gem} = 11.5 Hz, H-1'α), 4.56 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 4.08 (1H, d, J_{gem} = 11.5 Hz, H-1'β), 3.96 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.77 (3H, s, **CH_3**O-C6), 3.67 (1H, d, $J_{11,1}$ = 5.6 Hz, H-11), 3.22 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.3 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.37 (3H, s, **CH_3**-C8), 1.52 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.94 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH_3**-C10).

^{13}C-NMR (75MHz, $CDCl_3$): δ 164.36 (**C**O$CHCl_2$), 160.97 (C6), 144.66 (C4b), 136.71 (C8), 136.33 (C8a), 115.03 (C5), 108.98 (C7), 91.14 (C3), 82.71 (C11), 80.56 (C9), 74.05 (C1), 68.37 (C1'), 64.72 (CO**C**HCl_2), 55.63 (**CH_3**O-C6), 44.10 (C9a), 41.37 (C4a), 40.23 (C4), 38.17 (C10), 18.96 (**CH_3**-C8), 14.74 (**CH_3**-C10).

LRMS (*m/z*): 432 (M^+, $^{37}Cl_2$, 9%), 430 (M^+, ^{37}Cl ^{35}Cl, 44%), 428 (M^+, $^{35}Cl_2$, 60%), 392 (21), 347 (16), 301 (19), 271 (9), 254 (18), 239 (23), 225 (48), 213 (15), 200 (34), 189 (91), 173 (22), 160 (100), 128 (13), 115 (17), 95 (7), 83 (15).

HRMS (EI): Found 432.0721 (M^+, $^{37}Cl_2$), $C_{20}H_{22}O_6Cl_2$ requires 432.0734; Found 430.0753 (M^+, ^{37}Cl ^{35}Cl), $C_{20}H_{22}O_6Cl_2$ requires 430.0764; Found 428.0787 (M^+, $^{35}Cl_2$), $C_{20}H_{22}O_6Cl_2$ requires 428.0793.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3391 (br), 2959 (w), 2853 (w), 2840 (w), 1750 (s), 1600 (m), 1482 (w), 1456 (w), 1382 (w), 1301 (m), 1278 (m), 1193 (w), 1180 (w), 1141 (s), 1100 (w), 1079 (w), 1054 (w), 999 (w), 949 (w), 865 (w), 814 (w), 746 (w).

(1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,3,4,4a,9,9a-hexahydro-4-hydroxymethyl-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3-ol.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.90 (1H, s, H-7), 6.62 (1H, s, H-5), 5.30 (1H, s, H-3), 5.29 (1H, d, $J_{9,9a}$ = 5.2 Hz, H-9), 4.55 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.5 Hz, H-1), 4.00 (1H, d, $J_{4a,9a}$ = 8.8 Hz, H-4a), 3.79 (3H, s, **CH_3**O-C6), 3.62 (1H, d, $J_{11,1}$ = 5.5 Hz, H-11), 3.51 (1H, d, J_{gem} = 10.3 Hz, H-1'α), 3.21 (1H, ddd, $J_{9a,4a}$ = 8.9 Hz, $J_{9a,1}$ = 5.5 Hz, $J_{9a,9}$ = 5.2 Hz, H-9a), 2.95 (1H, d, $J_{,gem}$ = 10.2 Hz, H-1'β), 2.36 (3H, s, **CH_3**-C8), 1.38 (1H, q, $J_{10,Me}$ = 7.7 Hz, H-10), 0.82 (3H, d, $J_{Me,10}$ = 7.6 Hz, **CH_3**-C10).

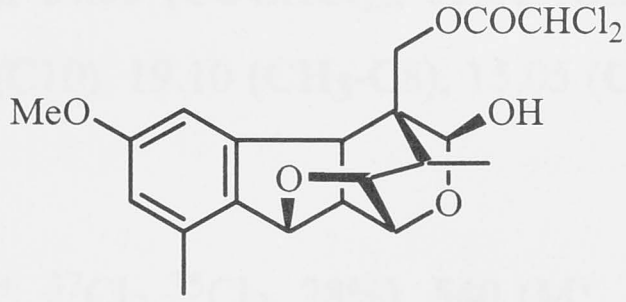
^{13}C-NMR (75MHz, $CDCl_3$): δ 160.91 (C6), 145.24 (C4b), 136.25 (C8), 135.73 (C8a), 114.97 (C5), 108.90 (C7), 93.28 (C3), 82.59 (C11), 80.46 (C9), 74.13 (C1), 64.18 (C1'), 55.47 (**CH_3**O-C6), 43.69 (C9a), 41.19 (C4a), 38.40 (C10), 37.27 (C4), 18.73 (**CH_3**-C8), 13.95 (**CH_3**-C10).

LRMS (*m/z*): 318 (M^+, 100%), 300 (6), 271 (6), 254 (10), 243 (19), 225 (23), 213 (20), 200 (27), 189 (67), 173 (24), 160 (86), 149 (16), 128 (16), 115 (25), 83 (23), 69 (17).

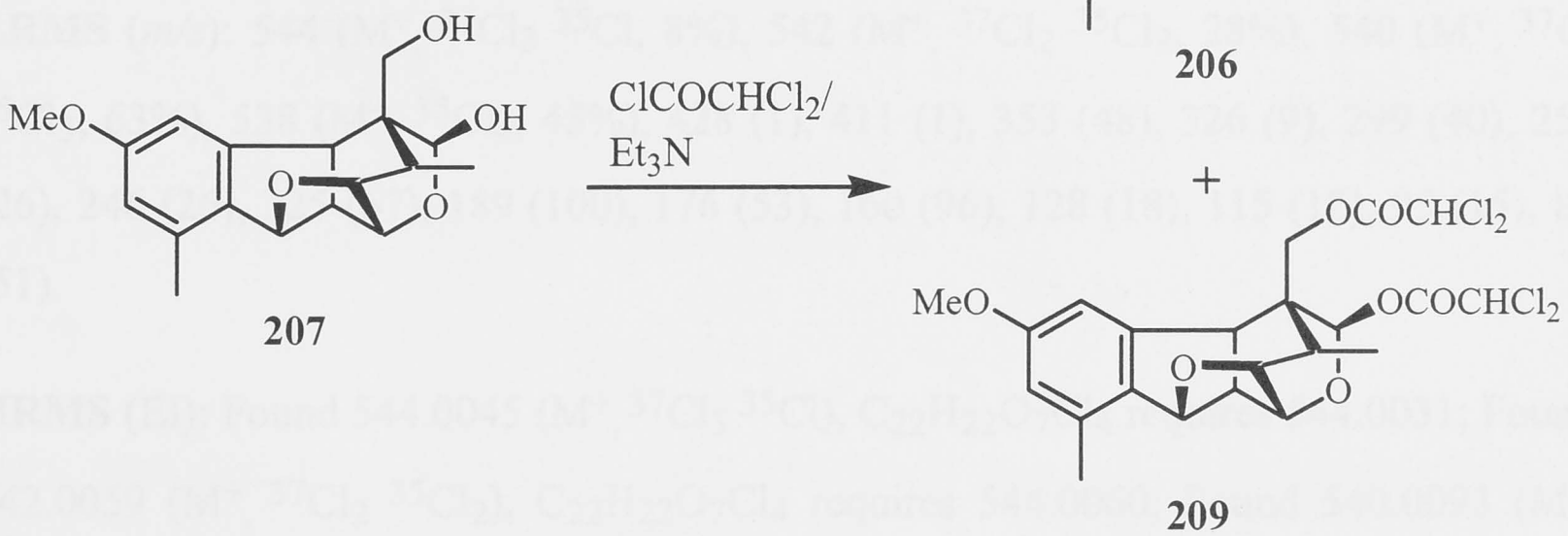
HRMS (EI): Found 318.1470 (M^+), $C_{18}H_{22}O_5$ requires 318.1467.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3352 (br), 2959 (w), 1607 (m), 1481 (m), 1465 (w), 1377 (w), 1344 (w), 1276 (w), 1231 (w), 1201 (w), 1139 (s), 1100 (w), 1079 (m), 1052 (m), 1014 (m), 943 (w), 857 (w), 754 (w).

(1*RS*, 3*SR*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-Dichloroacetoxymethyl-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran-3-ol and (1*RS*, 3*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-3-Dichloroacetoxy-4-dichloroacetoxymethyl-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran.



206



207 **209**

Dichloroacetyl chloride (4 µl, 0.042 mmol) in dichloromethane (100 µl) was added dropwise over 20 minutes to the diol **207** (12 mg, 0.038 mmol) and pyridine (3 µl, 0.042 mmol) in dichloromethane (1 ml) at –78°C. Stirring was continued at –78°C for 1 hour. Methanol (1 ml) was added and the solution was stirred at room temperature for 5 minutes. The solvent was removed under reduced pressure and the residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the acetate **206** (10 mg, 62%), the diacetate **209** (2 mg, 10%) and starting material (1 mg), each as a colourless oil.

(1*RS*, 3*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-3-Dichloroacetoxy-4-dichloroacetoxymethyl-8,10-dimethyl-9,11-epoxy-1,4,4a,9a-tetrahydro-3-hydroxy-6-methoxy-1,4-ethanoindeno[2,1-*c*]pyran.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.65 (1H, s, H-7), 6.55 (1H, s, H-5), 6.26 (1H, s, H-3), 6.03 (1H, s, COC**H**Cl_2), 6.02 (1H, s, COC**H**Cl_2), 5.32 (1H, d, $J_{9,9a}$ = 5.1 Hz, H-9), 4.68 (1H, dd, $J_{1,9a}$ = 5.5 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 4.46 (1H, d, J_{gem} = 11.8 Hz, H-1'α), 4.32 (1H, d, J_{gem} = 11.8 Hz, H-1'β), 3.92 (1H, d, $J_{4a,9a}$ = 8.7 Hz, H-4a), 3.76 (3H, s, **CH_3**O-C6), 3.75 (1H, d, $J_{11,1}$ = 5.6 Hz, H-11), 3.29 (1H, ddd, $J_{9a,4a}$ = 8.7 Hz, $J_{9a,1}$ = 5.5 Hz,

$J_{9a,9}$ = 5.1 Hz, H-9a), 2.37 (3H, s, **CH$_3$**-C8), 1.65 (1H, q, $J_{10,Me}$ = 7.7 Hz, H-10), 1.02 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH$_3$**-C10).

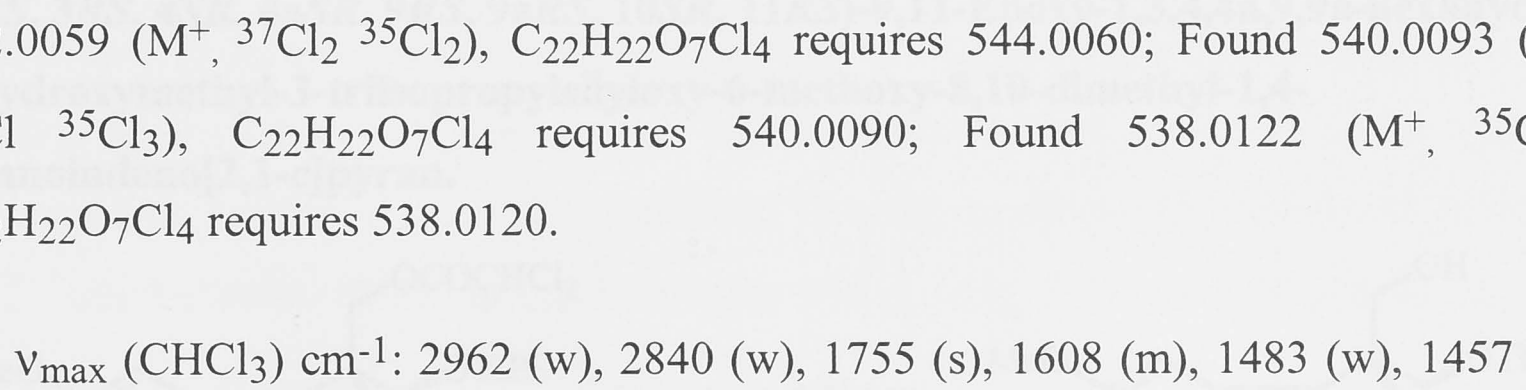
^{13}C-NMR (75MHz, $CDCl_3$): δ 164.00 (2x **C**OCHCl$_2$), 161.12 (C6), 143.13 (C4b), 136.57 (C8), 136.42 (C8a), 115.83 (C5), 108.31 (C7), 95.94 (C3), 82.86 (C11), 80.28 (C9), 74.71 (C1), 68.64 (C1'), 64.79 (CO**C**HCl$_2$), 64.39 (CO**C**HCl$_2$), 55.80 (**CH$_3$**O-C6), 43.93 (C9a), 41.37 (C4a), 40.87 (C4), 38.81 (C10), 19.10 (**CH$_3$**-C8), 15.05 (**CH$_3$**-C10).

LRMS (*m/z*): 544 (M^+, $^{37}Cl_3$ ^{35}Cl, 8%), 542 (M^+, $^{37}Cl_2$ $^{35}Cl_2$, 28%), 540 (M^+, ^{37}Cl $^{35}Cl_3$, 63%), 538 (M^+, $^{35}Cl_4$, 45%), 428 (1), 411 (1), 353 (48), 326 (9), 299 (40), 255 (26), 246 (26), 225 (67), 189 (100), 176 (53), 160 (96), 128 (18), 115 (10), 95 (15), 83 (51).

HRMS (EI): Found 544.0045 (M^+, $^{37}Cl_3$ ^{35}Cl), $C_{22}H_{22}O_7Cl_4$ requires 544.0031; Found 542.0059 (M^+, $^{37}Cl_2$ $^{35}Cl_2$), $C_{22}H_{22}O_7Cl_4$ requires 544.0060; Found 540.0093 (M^+, ^{37}Cl $^{35}Cl_3$), $C_{22}H_{22}O_7Cl_4$ requires 540.0090; Found 538.0122 (M^+, $^{35}Cl_4$), $C_{22}H_{22}O_7Cl_4$ requires 538.0120.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2962 (w), 2840 (w), 1755 (s), 1608 (m), 1483 (w), 1457 (w), 1379 (w), 1340 (w), 1316 (m), 1298 (m), 1279 (m), 1263 (m), 1236 (w), 1209 (w), 1193 (w), 1171 (w), 1141 (s), 1113 (m), 1075 (w), 1055 (w), 1001 (m), 942 (w), 907 (w), 815 (w), 745 (w).

(1*RS*, 3*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-4-Dichloroacetoxymethyl-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-3-triisopropylsilyloxy-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran.



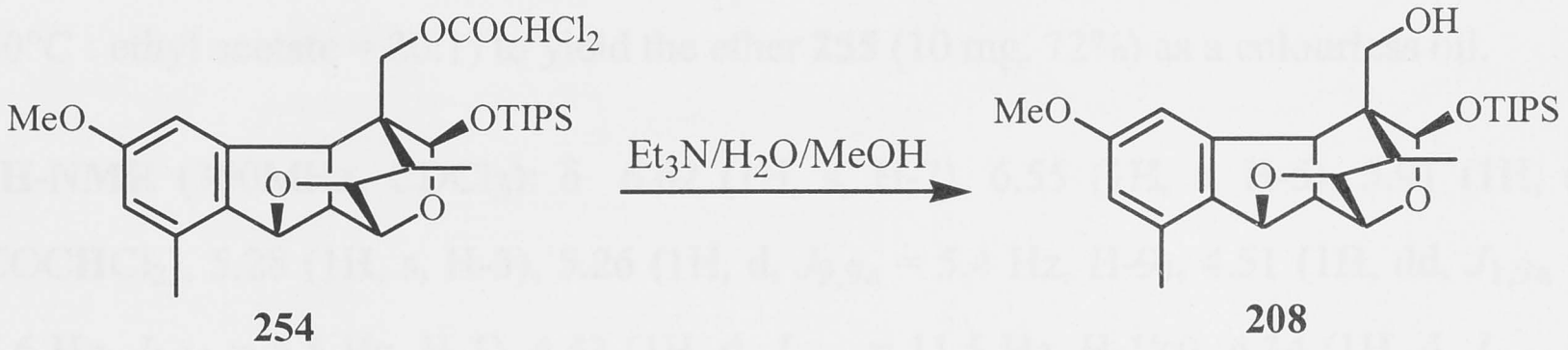
206 **254**

Triisopropylsilyl trifluoromethanesulfonate (62 µl, 0.23 mmol) was added dropwise to the hemi-acetal **206** (10 mg, 0.023 mmol) and *N,N*-diisopropylethylamine (43 µl, 0.25

mmol) in dichloromethane (1 ml). Stirring was continued at room temperature for 16 hour. Methanol (1 ml) was added and the solvent was removed under reduced pressure. The residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 20:1) to yield the ether **254** (2 mg, 15%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.62 (1H, s, H-7), 6.53 (1H, s, H-5), 5.88 (1H, s, COC**H**Cl_2), 5.28 (1H, s, H-3), 5.26 (1H, d, $J_{9,9a}$ = 5.4 Hz, H-9), 4.53 (1H, dd, $J_{1,9a}$ = 5.6 Hz, $J_{1,11}$ = 5.5 Hz, H-1), 4.40 (1H, d, J_{gem} = 11.4 Hz, H-1'α), 4.34 (1H, d, J_{gem} = 11.4 Hz, H-1'β), 3.85 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.77 (3H, s, **CH_3**O-C6), 3.67 (1H, d, $J_{11,1}$ = 5.1 Hz, H-11), 3.14 (1H, ddd, $J_{9a,4a}$ = 8.9 Hz, $J_{9a,1}$ = 5.6 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.37 (3H, s, **CH_3**-C8), 1.58 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 1.09-1.05 (21H, m, **C_9H_{21}**-Si), 0.98 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH_3**-C10).

(1*RS*, 3*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-Epoxy-1,3,4,4a,9,9a-hexahydro-4-hydroxymethyl-3-triisopropylsilyloxy-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran.



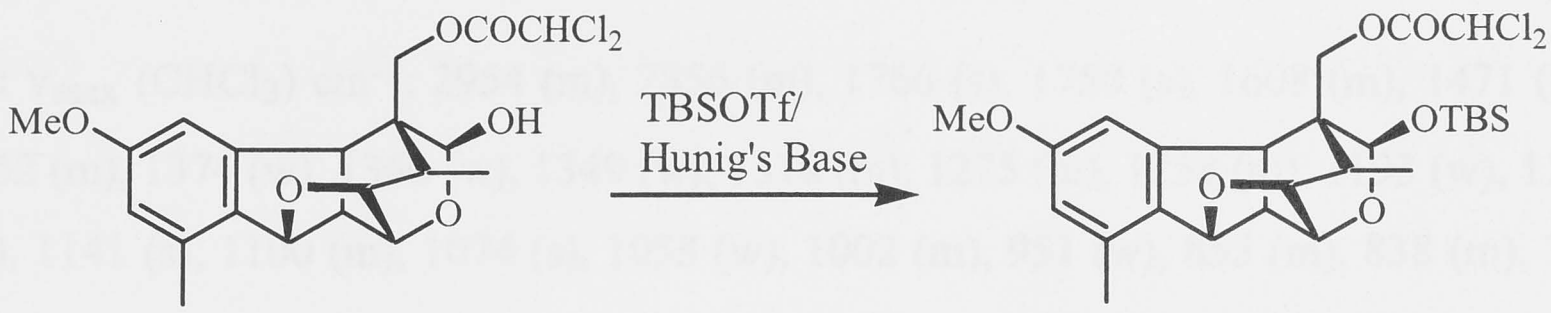
254 **208**

The dichloroacetate **254** (2 mg, 0.003 mmol), triethylamine (4 µl, 0.03 mmol) and water (1 µl) were stirred in methanol (1 ml) for 16 hours. The mixture was diluted with ethyl acetate (10 ml), washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 10:1) to afford the alcohol **208** (1 mg, 61%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.90 (1H, s, H-5), 6.64 (1H, s, H-7), 5.29 (1H, s, H-3), 5.25 (1H, d, $J_{9,9a}$ = 5.5 Hz, H-9), 4.51 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.7 Hz, H-1), 3.98 (1H, d, $J_{4a,9a}$ = 9.0 Hz, H-4a), 3.75 (3H, s, **CH_3**O-C6), 3.60 (1H, d, $J_{11,1}$ = 5.7 Hz, H-11), 3.40 (1H, d, J_{gem} = 10.8 Hz, H-1'α), 3.14 (1H, ddd, $J_{9a,4a}$ = 9.0 Hz, $J_{9a,1}$ = 5.4 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.90 (1H, d, J_{gem} = 10.8 Hz, H-1'β), 2.39 (3H, s, **CH_3**-C8),

1.35 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 1.09-1.05 (21H, m, **C$_9$H$_{21}$**-Si), 0.82 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH$_3$**-C10).

(1*RS*, 3*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-3-(*tert.*-Butyldimethylsilyloxymethyl) -4-dichloroacetoxymethyl-9,11-epoxy-1,3,4,4a,9,9a-hexahydro-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran.



206 **255**

tert.-Butyldimethylsilyl trifluoromethanesulfonate (30 µl, 0.13 mmol) was added dropwise to the alcohol **206** (11 mg, 0.26 mmol) and *N,N*-diisopropylethylamine (46 µl, 0.26 mmol) in dichloromethane (1 ml). Stirring was continued at room temperature for 1 hour. Methanol (1 ml) was added and the solvent was removed under reduced pressure. The residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 20:1) to yield the ether **255** (10 mg, 72%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.62 (1H, s, H-7), 6.55 (1H, s, H-5), 5.91 (1H, s, COC**H**Cl$_2$), 5.28 (1H, s, H-3), 5.26 (1H, d, $J_{9,9a}$ = 5.4 Hz, H-9), 4.51 (1H, dd, $J_{1,9a}$ = 5.6 Hz, $J_{1,11}$ = 5.5 Hz, H-1), 4.43 (1H, d, J_{gem} = 11.5 Hz, H-1'α), 4.34 (1H, d, J_{gem} = 11.7 Hz, H-1'β), 3.85 (1H, d, $J_{4a,9a}$ = 8.9 Hz, H-4a), 3.77 (3H, s, **CH$_3$**O-C6), 3.66 (1H, d, $J_{11,1}$ = 5.5 Hz, H-11), 3.14 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 5.5 Hz, $J_{9a,9}$ = 5.5 Hz, H-9a), 2.36 (3H, s, **CH$_3$**-C8), 1.58 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.98 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH$_3$**-C10), 0.93 (9H, s, **(CH$_3$)$_3$**-C), 0.18 (3H, s, **CH$_3$**-Si), 0.12 (3H, s, **CH$_3$**-Si).

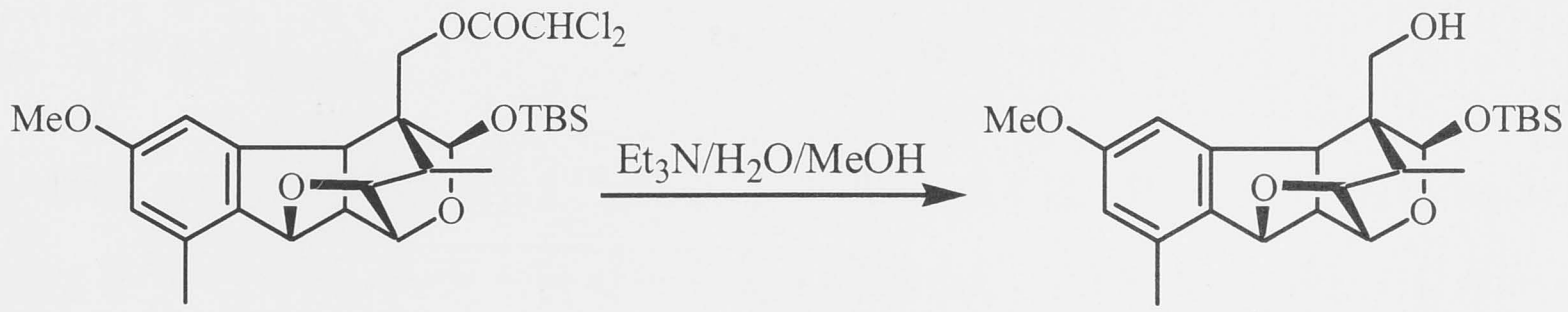
^{13}C-NMR (75MHz, $CDCl_3$): δ 164.20 (**C**OCHCl$_2$), 160.88 (C6), 144.96 (C4b), 136.80 (C8), 136.22 (C8a), 115.23 (C5), 108.57 (C7), 90.73 (C3), 82.60 (C11), 81.01 (C9), 73.79 (C1), 70.02 (C1'), 64.43 (CO**C**HCl$_2$), 55.67 (**CH$_3$**O-C6), 44.22 (C9a), 42.31 (C4), 41.95 (C4a), 38.53 (C10), 26.05 (**(CH$_3$)$_3$**-C), 18.93 (**CH$_3$**-C8), 18.20 ((CH$_3$)$_3$-**C**), 15.27 (**CH$_3$**-C10), -3.83 (**CH$_3$**-Si), -4.60 (**CH$_3$**-Si).

LRMS (*m/z*): 432 (M^+ - C_4H_9, $^{37}Cl_2$, 9%), 430 (M^+ - C_4H_9, ^{37}Cl ^{35}Cl, 44%), 428 (M^+ - C_4H_9, $^{35}Cl_2$, 60%), 392 (21), 347 (16), 301 (19), 271 (9), 254 (18), 239 (23), 225 (48), 213 (15), 200 (34), 189 (91), 173 (22), 160 (100), 128 (13), 115 (17), 95 (7), 83 (15).

HRMS (EI): Found 489.0911 (M^+ - C_4H_9, $^{37}Cl_2$), $C_{22}H_{27}O_6SiCl_2$ requires 489.0895; Found 487.0917 (M^+ - C_4H_9, ^{37}Cl ^{35}Cl), $C_{22}H_{27}O_6SiCl_2$ requires 487.0924; Found 485.0968 (M^+ - C_4H_9, $^{35}Cl_2$), $C_{22}H_{27}O_6SiCl_2$ requires 485.0954.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2954 (m), 2856 (m), 1766 (s), 1750 (s), 1608 (m), 1471 (m), 1462 (m), 1374 (w), 1360 (w), 1349 (w), 1318 (m), 1275 (m), 1258 (m), 1193 (w), 1165 (w), 1141 (s), 1100 (m), 1074 (s), 1058 (w), 1002 (m), 951 (w), 855 (m), 838 (m), 780 (w).

(1*RS*, 3*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-3-(*tert.*-Butyldimethylsilyloxymethyl) -9,11-epoxy-1,3,4,4a,9,9a-hexahydro-4-hydroxymethyl-6-methoxy-8,10-dimethyl-1,4-ethanoindeno[2,1-*c*]pyran.



255 **210**

The dichloroacetate **255** (10 mg, 0.018 mmol), triethylamine (20 µl, 0.144 mmol) and water (5 µl) were stirred in methanol (1 ml) for 16 hours. The mixture was diluted with ethyl acetate (20 ml), washed with brine (2x5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 10:1) to afford the alcohol **210** (7 mg, 90%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.91 (1H, s, H-5), 6.62 (1H, s, H-7), 5.29 (1H, s, H-3), 5.28 (1H, d, $J_{9,9a}$ = 5.4 Hz, H-9), 4.51 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 5.6 Hz, H-1), 3.97 (1H, d, $J_{4a,9a}$ = 9.1 Hz, H-4a), 3.79 (3H, s, **CH_3**O-C6), 3.60 (1H, d, $J_{11,1}$ = 5.5 Hz, H-11), 3.44 (1H, d, J_{gem} = 11.1 Hz, H-1'α), 3.14 (1H, ddd, $J_{9a,4a}$ = 9.1 Hz, $J_{9a,1}$ = 5.5 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.95 (1H, d, J_{gem} = 11.0 Hz, H-1'β), 2.36 (3H, s, **CH_3**-C8),

1.35 (1H, q, $J_{10,Me}$ = 7.6 Hz, H-10), 0.95 (9H, s, **(CH$_3$)$_3$**-C), 0.82 (3H, d, $J_{Me,10}$ = 7.7 Hz, **CH$_3$**-C10), 0.23 (3H, s, **CH$_3$**-Si), 0.22 (3H, s, **CH$_3$**-Si).

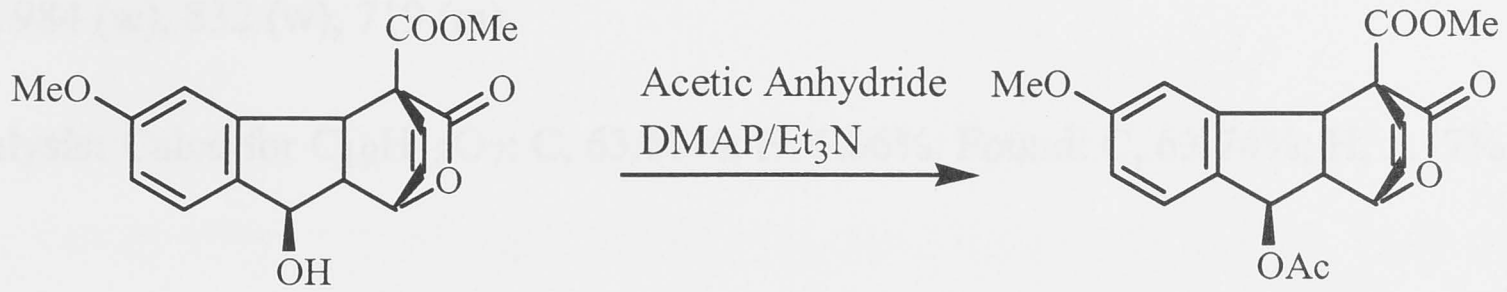
^{13}C-NMR (75MHz, $CDCl_3$): δ 160.87 (C6), 145.16 (C4b), 136.29 (C8), 135.66 (C8a), 115.02 (C5), 108.73 (C7), 93.52 (C3), 82.52 (C11), 80.57 (C9), 74.14 (C1), 64.38 (C1'), 55.41 (**CH$_3$**O-C6), 43.63 (C9a), 41.52 (C4a), 38.30 (C10), 37.26 (C4), 25.84 ((**CH$_3$**)$_3$-C), 18.64 (**CH$_3$**-C8), 17.84 ((CH$_3$)$_3$-**C**), 14.06 (**CH$_3$**-C10), -3.65 (2x **CH$_3$**-Si).

LRMS (*m/z*): 432 (M^+, 1%), 375 (40), 329 (6), 283 (16), 275 (12), 265 (14), 255 (23), 237 (12), 225 (26), 213 (21), 197 (16), 173 (20), 169 (22), 159 (100), 149 (24), 138 (26), 110 (27), 97 (33), 83 (43), 77 (29), 57 (42).

HRMS (EI): Found 432.2335 (M^+), $C_{24}H_{36}O_5Si$ requires 432.2332.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3400 (br), 2955 (m), 2928 (m), 2855 (w), 1608 (m), 1598 (m), 1481 (w), 1463 (m), 1375 (w), 1347 (w), 1317 (w), 1275 (w), 1258 (w), 1231 (w), 1200 (w), 1139 (s), 1112 (w), 1099 (w), 1079 (m), 1070 (m), 1053 (m), 1025 (w), 996 (w), 856 (w), 838 (w).

Methyl (1*SR*, 4*RS*, 4a*SR*, 9*RS*, 9a*RS*)-9-acetoxy-1,4,4a,9a-tetrahydro-6-methoxy-3-oxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



130 **213**

Acetic anhydride (130 µl, 1.38 mmol) was added to the alcohol **130** (176 mg, 0.56 mmol), DMAP (1 mg) and triethylamine (310 µl, 2.22 mmol) in dichloromethane (10 ml) and stirred at room temperature for 16 hours. The solution was acidified with 2M HCl (10 ml) and extracted with dichloromethane (3x40 ml). The combined organic phase was washed with water (15 ml), brine (15 ml) and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C: ethyl acetate = 3:1) to yield the acetate **213** (193 mg, 97%). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p. : 139-141°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.15 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.83 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 6.51 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.42 – 6.35 (2H, m, H-10, H-11), 6.29 (1H, d, $J_{9,9a}$ = 9.1 Hz, H-9), 5.18 (1H, ddd, $J_{1,9a}$ = 4.3 Hz, $J_{1,11}$ = 4.2 Hz, $J_{1,10}$ = 2.3 Hz, H-1), 4.31 (1H, d, $J_{4a,9a}$ = 8.2 Hz, H-4a), 4.05 (3H, s, COO**CH$_3$**), 3.76 (3H, s, **CH$_3$**O-C6), 3.72 (1H, ddd, $J_{9a,4a}$ = 8.2 Hz, $J_{9a,9}$ = 9.1 Hz, $J_{9a,1}$ = 4.3 Hz, H-9a), 2.18 (3H, s, OCO**CH$_3$**).

^{13}C-NMR (75MHz, $CDCl_3$): δ 171.47 (O**C**OCH$_3$), 170.53 (C3), 168.84 (C12), 161.68 (C6), 141.24 (C4b), 134.30 (C8a), 130.76 (C11), 130.57 (C10), 126.88 (C8), 115.96 (C5), 109.14 (C7), 75.54 (C9), 75.33 (C1), 60.54 (C4), 55.92 (**CH$_3$**O-C6), 53.82 (COO**CH$_3$**), 47.06 (C9a), 46.55 (C4a), 21.62 (OCO**CH$_3$**).

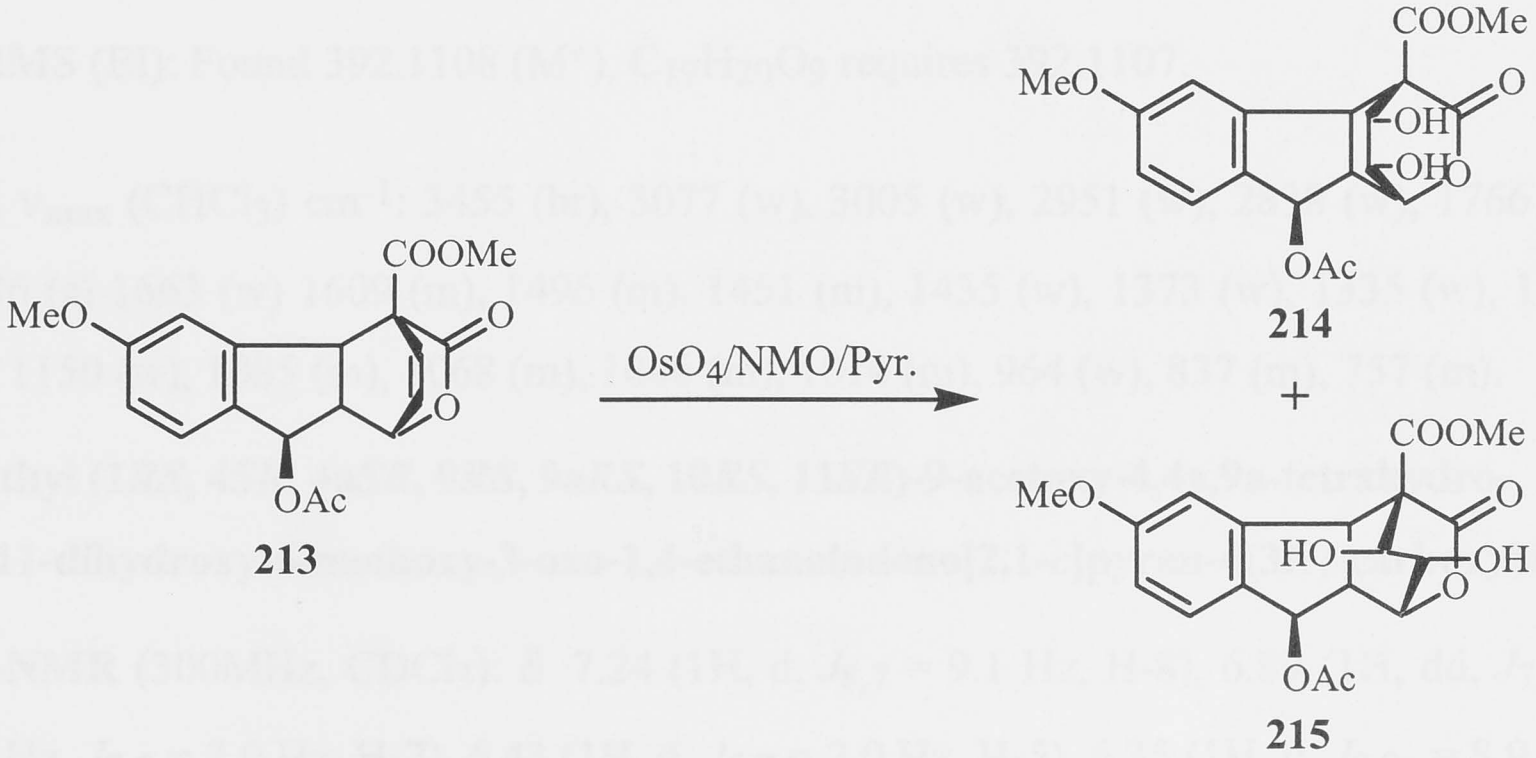
LRMS (*m/z*): 358 (M^+, 25%), 316 (3), 299 (3), 267 (3), 254 (14), 214 (11), 211 (24), 205 (22), 162 (100), 145 (30), 135 (12), 102 (9), 77 (9).

HRMS (EI): Found 358.1049 (M^+), $C_{19}H_{18}O_7$ requires 358.1053.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3014 (w), 2952 (w), 1762 (s), 1730 (s), 1614 (w), 1588 (w), 1439 (w), 1371 (w), 1285 (m), 1274 (m), 1262 (m), 1233 (s), 1123 (m), 1074 (m), 1029 (w), 984 (w), 832 (w), 719 (m).

Analysis: Calcd for $C_{19}H_{18}O_7$: C, 63.68%; H, 5.06%. Found: C, 63.74%; H, 5.17%.

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*SR*)-9-acetoxy-4,4a,9a-tetrahydro-10,11-dihydroxy-6-methoxy-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate and Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-9-acetoxy-4,4a,9a-tetrahydro-10,11-dihydroxy-6-methoxy-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



A catalytic amount of osmium tetroxide (1 mg) was added to the alkene **213** (25 mg, 0.07 mmol), *N*-methylmorpholine oxide (31 mg, 0.265 mmol), pyridine (1 ml) and water (100 µl) in acetone (2.5 ml) and stirred for 16 hours. The solvent was removed under reduced pressure and the residue was redissolved in chloroform (50 ml). The organic phase was washed with water (5 ml), brine (10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (Chloroform : methanol = 5:1) to afford the *cis* diol **214** (9 mg, 33%) and the *trans* diol **215** (10 mg, 37%), both as colourless oils.

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*SR*)-9-acetoxy-4,4a,9a-tetrahydro-10,11-dihydroxy-6-methoxy-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.18 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.85 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 6.59 (1H, d, $J_{5,7}$ = 2.1 Hz, H-5), 6.39 (1H, d, $J_{9,9a}$ = 8.9 Hz, H-9), 5.00 (1H, d, $J_{11,10}$ = 7.6 Hz, H-11), 4.88 (1H, d, $J_{1,9a}$ = 3.5 Hz, H-1), 4.69 (1H, d,

$J_{10,11}$ = 7.6 Hz, H-10), 4.20 (1H, d, $J_{4a,9a}$ = 9.3 Hz, H-4a), 3.97 (3H, s, COO**CH$_3$**), 3.75 (3H, s, **CH$_3$**O-C6), 3.44 (1H, ddd, $J_{9a,4a}$ = 9.3 Hz, $J_{9a,1}$ = 3.5 Hz, $J_{9a,9}$ = 8.9 Hz, H-9a), 2.19 (3H, s, OCO**CH$_3$**).

^{13}C-NMR (75MHz, $CDCl_3$): δ 171.71 (O**C**OCH$_3$), 170.24 (C3), 169.79 (C12), 161.27 (C6), 140.45 (C4b), 133.26 (C8a), 126.64 (C8), 116.37 (C5), 109.85 (C7), 88.89 (C11), 86.46 (C10), 83.69 (C1), 75.70 (C9), 60.17 (C4), 55.91 (**CH$_3$**O-C6), 53.33 (COO**CH$_3$**), 46.08 (C9a), 45.08 (C4a), 21.67 (OCO**CH$_3$**).

LRMS (*m/z*): 392 (M^+, 1%), 390 (1), 330 (3), 284 (4), 268 (100), 254 (43), 237 (46), 209 (44), 195 (50), 181 (11), 166 (9), 152 (23), 138 (17), 79 (22), 60 (96).

HRMS (EI): Found 392.1108 (M^+), $C_{19}H_{20}O_9$ requires 392.1107.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3455 (br), 3077 (w), 3005 (w), 2951 (w), 2838 (w), 1766 (s), 1736 (s) 1663 (w) 1609 (m), 1496 (m), 1451 (m), 1435 (w), 1373 (w), 1335 (w), 1229 (s), 1150 (w), 1085 (m), 1068 (m), 1046 (m), 1014 (m), 964 (w), 837 (m), 757 (m).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-9-acetoxy-4,4a,9a-tetrahydro-10,11-dihydroxy-6-methoxy-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.24 (1H, d, $J_{8,7}$ = 9.1 Hz, H-8), 6.89 (1H, dd, $J_{7,8}$ = 9.1 Hz, $J_{7,5}$ = 2.0 Hz, H-7), 6.43 (1H, d, $J_{5,7}$ = 2.0 Hz, H-5), 6.35 (1H, d, $J_{9,9a}$ = 8.9 Hz, H-9), 4.63 (1H, d, $J_{1,9a}$ = 3.6 Hz, H-1), 4.22 (1H, d, $J_{4a,9a}$ = 9.2 Hz, H-4a), 4.17 (1H, d, $J_{10,11}$ = 7.6 Hz, H-10), 4.06 (3H, s, COO**CH$_3$**), 4.00 (1H, d, $J_{11,10}$ = 7.6 Hz, H-11), 3.79 (3H, s, **CH$_3$**O-C6), 3.44 (1H, ddd, $J_{9a,4a}$ = 9.2 Hz, $J_{9a,1}$ = 3.6 Hz, $J_{9a,9}$ = 8.9 Hz, H-9a), 2.23 (3H, s, OCO**CH$_3$**).

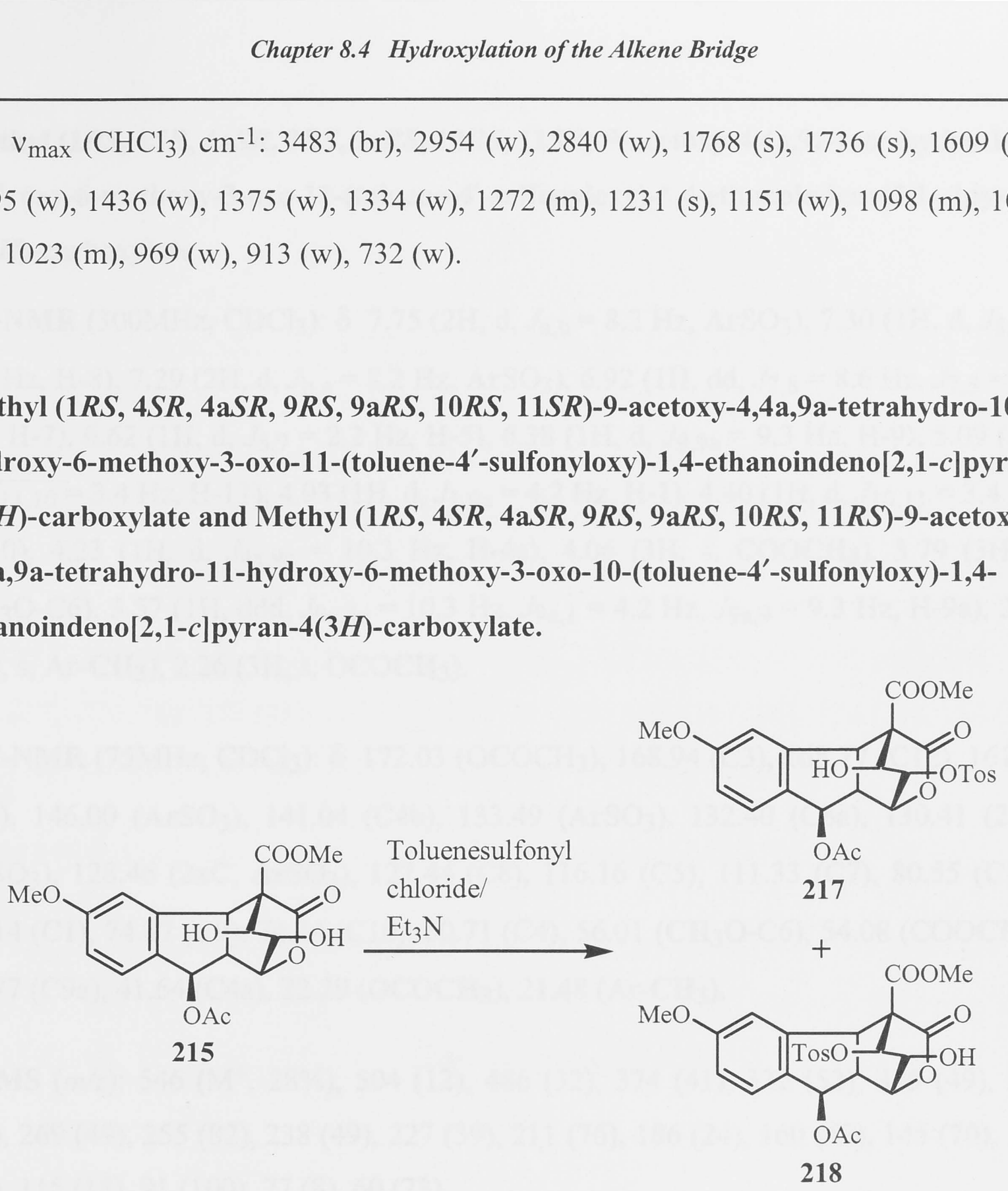
^{13}C-NMR (75MHz, $CDCl_3$): δ 171.54 (O**C**OCH$_3$), 171.39 (C3), 169.09 (C12), 161.59 (C6), 139.28 (C4b), 133.04 (C8a), 127.26 (C8), 115.66 (C5), 110.15 (C7), 82.75 (C1), 75.30 (C9), 66.26 (C11), 64.22 (C10), 59.72 (C4), 56.03 (**CH$_3$**O-C6), 54.19 (COO**CH$_3$**), 43.25 (C9a), 43.19 (C4a), 21.43 (OCO**CH$_3$**).

LRMS (*m/z*): 392 (M^+, 36%), 374 (12), 350 (25), 332 (77), 318 (29), 301 (24), 288 (26), 270 (39), 256 (43), 242 (25), 227 (50), 211 (68), 199 (33), 186 (30), 175 (68), 145 (100), 130 (36), 115 (43), 102 (30), 91 (17), 77 (21), 60 (13).

HRMS (EI): Found 392.1107 (M^+), $C_{19}H_{20}O_9$ requires 392.1107.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3483 (br), 2954 (w), 2840 (w), 1768 (s), 1736 (s), 1609 (w), 1495 (w), 1436 (w), 1375 (w), 1334 (w), 1272 (m), 1231 (s), 1151 (w), 1098 (m), 1063 (s), 1023 (m), 969 (w), 913 (w), 732 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-9-acetoxy-4,4a,9a-tetrahydro-10-hydroxy-6-methoxy-3-oxo-11-(toluene-4′-sulfonyloxy)-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate and Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*RS*)-9-acetoxy-4,4a,9a-tetrahydro-11-hydroxy-6-methoxy-3-oxo-10-(toluene-4′-sulfonyloxy)-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



para-Toluenesulfonyl chloride (30 mg, 0.11 mmol) was added to the diol **215** (30 mg, 0.077 mmol) and triethylamine (27 µl, 0.19 mmol) in dichloromethane (2ml) and stirred for 12 hours at room temperature. The mixture was acidified with 2M HCl (1 ml) and extracted with dichloromethane (3x 5ml). The combined organic phase was washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 1:1) to afford the major product **217** (24 mg, 57%) and the minor product **218** (18 mg, 27%), both as colourless oils.

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*SR*)-9-acetoxy-4,4a,9a-tetrahydro-10-hydroxy-6-methoxy-3-oxo-11-(toluene-4′-sulfonyloxy)-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.75 (2H, d, $J_{a,b}$ = 8.2 Hz, **Ar**SO_3), 7.30 (1H, d, $J_{8,7}$ = 8.6 Hz, H-8), 7.29 (2H, d, $J_{b,a}$ = 8.2 Hz, **Ar**SO_3), 6.92 (1H, dd, $J_{7,8}$ = 8.6 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 6.62 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 6.38 (1H, d, $J_{9,9a}$ = 9.3 Hz, H-9), 5.09 (1H, d, $J_{11,10}$ = 3.4 Hz, H-11), 4.93 (1H, d, $J_{1,9a}$ = 4.2 Hz, H-1), 4.40 (1H, d, $J_{10,11}$ = 3.4 Hz, H-10), 4.23 (1H, d, $J_{4a,9a}$ = 10.3 Hz, H-4a), 4.06 (3H, s, COO**C**$\mathbf{H_3}$), 3.79 (3H, s, **C**$\mathbf{H_3}$O-C6), 3.57 (1H, ddd, $J_{9a,4a}$ = 10.3 Hz, $J_{9a,1}$ = 4.2 Hz, $J_{9a,9}$ = 9.3 Hz, H-9a), 2.43 (3H, s, Ar-**C**$\mathbf{H_3}$), 2.26 (3H, s, OCO**C**$\mathbf{H_3}$).

^{13}C-NMR (75MHz, $CDCl_3$): δ 172.03 (O**C**OCH_3), 168.94 (C3), 168.77 (C12), 161.44 (C6), 146.00 (**Ar**SO_3), 141.04 (C4b), 133.49 (**Ar**SO_3), 132.40 (C8a), 130.41 (2xC, **Ar**SO_3), 128.46 (2xC, **Ar**SO_3), 127.44 (C8), 116.16 (C5), 111.33 (C7), 80.55 (C11), 79.14 (C1), 74.87 (C9), 74.34 (C10), 60.71 (C4), 56.01 (**C**$\mathbf{H_3}$O-C6), 54.08 (COO**C**$\mathbf{H_3}$), 43.77 (C9a), 41.64 (C4a), 22.29 (OCO**C**$\mathbf{H_3}$), 21.48 (Ar-**C**$\mathbf{H_3}$).

LRMS (*m/z*): 546 (M^+, 28%), 504 (12), 486 (32), 374 (41), 332 (52), 325 (49), 286 (23), 269 (49), 255 (82), 238 (49), 227 (39), 211 (76), 186 (24), 160 (52), 145 (70), 139 (20), 115 (18), 91 (100), 77 (8), 60 (23).

HRMS (EI): Found 546.1193 (M^+), $C_{26}H_{26}O_{11}S$ requires 546.1196.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3455 (br), 2937 (w), 1767 (s), 1740 (s), 1715 (s), 1613 (w), 1598 (w), 1495 (w), 1463 (w), 1434 (w), 1371 (m), 1333 (w), 1311 (w), 1264 (m), 1234 (s), 1193 (w), 1179 (m), 1152 (w), 1095 (s), 1080 (m), 1021 (w), 990 (w), 919 (w), 831 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*RS*, 11*RS*)-9-acetoxy-4,4a,9a-tetrahydro-11-hydroxy-6-methoxy-3-oxo-10-(toluene-4′-sulfonyloxy)-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.74 (2H, d, $J_{a,b}$ = 8.4 Hz, **Ar**SO_3), 7.30 (1H, d, $J_{8,7}$ = 8.9 Hz, H-8), 7.29 (2H, d, $J_{b,a}$ = 8.4 Hz, **Ar**SO_3), 6.96 (1H, dd, $J_{7,8}$ = 8.9 Hz, $J_{7,5}$ = 2.3 Hz, H-7), 6.40 (1H, d, $J_{5,7}$ = 2.1 Hz, H-5), 6.35 (1H, d, $J_{9,9a}$ = 8.9 Hz, H-9), 4.93 (1H, d, $J_{11,10}$ = 8.4 Hz, H-11), 4.82 (1H, d, $J_{1,9a}$ = 3.9 Hz, H-1), 4.24 (1H, d, $J_{10,11}$ = 8.4 Hz,

H-10), 4.21 (1H, d, $J_{4a,9a}$ = 9.8 Hz, H-4a), 4.04 (3H, s, COO**CH$_3$**), 3.81 (3H, s, **CH$_3$**O-C6), 3.50 (1H, ddd, $J_{9a,4a}$ = 9.8 Hz, $J_{9a,1}$ = 3.9 Hz, $J_{9a,9}$ = 8.9 Hz, H-9a), 2.43 (3H, s, Ar-**CH$_3$**), 2.28 (3H, s, OCO**CH$_3$**).

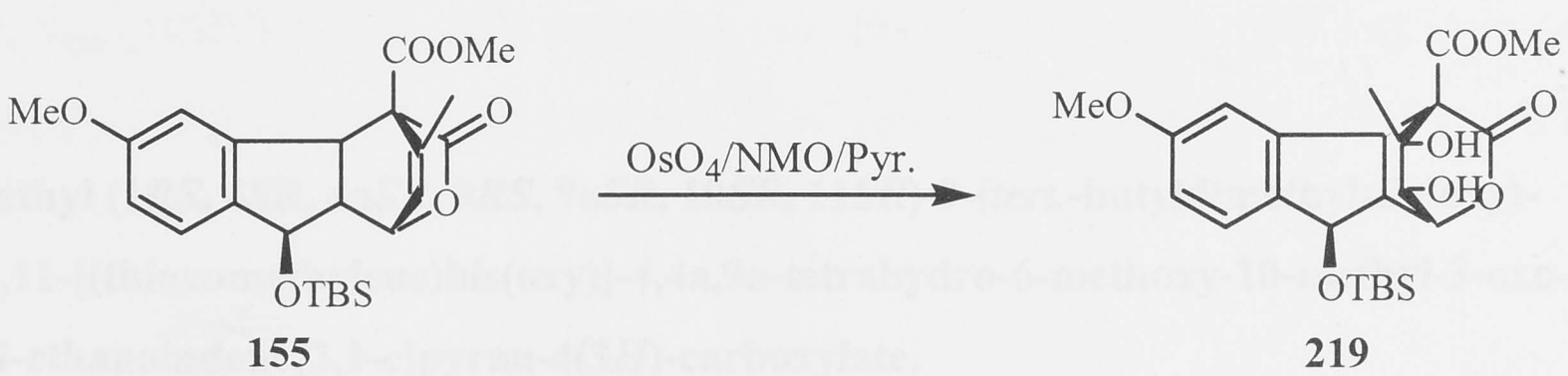
^{13}C-NMR (75MHz, $CDCl_3$): δ 171.71 (O**C**OCH$_3$), 170.48 (C3), 167.97 (C12), 161.80 (C6), 145.80 (**Ar**SO$_3$), 138.95 (C4b), 133.40 (**Ar**SO$_3$), 132.58 (C8a), 130.41 (2xC, **Ar**SO$_3$), 128.61 (2xC, **Ar**SO$_3$), 128.61 (C8), 116.28 (C7), 109.94 (C5), 79.98 (C1), 74.91 (C9), 70.75 (C11), 66.75 (C10), 66.74 (C4), 56.03 (**CH$_3$**O-C6), 54.22 (COO**CH$_3$**), 43.55 (C9a), 43.22 (C4a), 22.31 (OCO**CH$_3$**), 21.29 (Ar-**CH$_3$**).

LRMS (*m/z*): 546 (M^+, 8%), 504 (10), 486 (22), 374 (36), 332 (41), 325 (49), 299 (11), 287 (27), 270 (60), 238 (41), 227 (67), 211 (81), 195 (32), 187 (89), 174 (25), 162 (72), 145 (70), 130 (53), 121 (96), 100 (35), 91 (100), 77 (32), 65 (22), 57 (36).

HRMS (EI): Found 546.1187 (M^+), $C_{26}H_{26}O_{11}S$ requires 546.1196.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3519 (br), 3023 (w), 2954 (w), 2840 (w), 1773 (s), 1735 (s), 1608 (w), 1597 (w), 1495 (w), 1437 (w), 1370 (m), 1338 (w), 1308 (w), 1273 (w), 1227 (s), 1190 (w), 1176 (m), 1151 (w), 1100 (w), 1080 (m), 1015 (s), 972 (w), 872 (w), 813 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*SR*, 10*SR*, 11*SR*)-9-(*tert.*-butyldimethylsilyloxy)-4,4a,9a-tetrahydro-10,11-dihydroxy-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



155 **219**

A catalytic amount of osmium tetroxide (1 mg) was added to the alkene **155** (87 mg, 0.196 mmol), *N*-methylmorpholine oxide (160 mg, 1.37 mmol), pyridine (0.1 ml) in acetone (5 ml) and stirred for 16 hours. The mixture was filtered though a short pad of silica gel and the solvent was removed under reduced pressure. The residue was

chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to afford the diol **219** (84 mg, 90%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.22 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 6.91 (1H, dd, $J_{7,8}$ = 8.3 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 6.61 (1H, d, $J_{5,7}$ = 2.0 Hz, H-5), 5.37 (1H, d, $J_{9,9a}$ = 9.6 Hz, H-9), 4.72 (1H, d, $J_{1,9a}$ = 4.0 Hz, H-1), 4.28 (1H, s, H-11), 4.24 (1H, d, $J_{4a,9a}$ = 9.9 Hz, H-4a), 4.05 (3H, s, COO**CH$_3$**), 3.77 (3H, s, **CH$_3$**O-C6), 3.25 (1H, ddd, $J_{9a,4a}$ = 9.9 Hz, $J_{9a,1}$ = 4.0 Hz, $J_{9a,9}$ = 9.6 Hz, H-9a), 0.99 (9H, s, **(CH$_3$)$_3$**-C), 0.80 (3H, s, **CH$_3$**-C10), 0.25 (3H, s, **CH$_3$**-Si), 0.23 (3H, s, **CH$_3$**-Si).

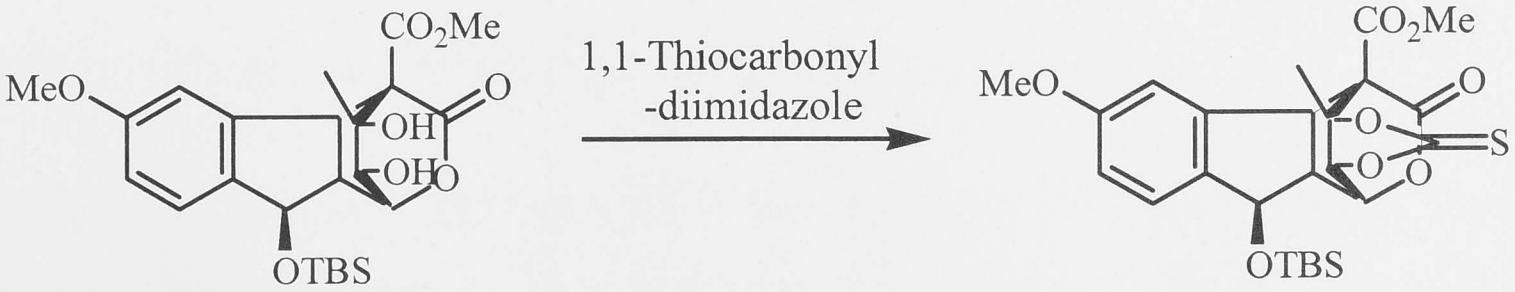
^{13}C-NMR (75MHz, $CDCl_3$): δ 171.92 (C3), 170.84 (C12), 160.33 (C6), 138.85 (C4b), 136.95 (C8a), 126.31 (C8), 115.15 (C5), 110.88 (C7), 83.18 (C11), 73.40 (C9), 72.79 (C1), 69.89 (C10), 64.32 (C4), 55.50 (**CH$_3$**O-C6), 53.33 (COO**CH$_3$**), 44.12 (C9a), 41.18 (C4a), 25.80 (**(CH$_3$)$_3$**-C), 18.13 ((CH$_3$)$_3$-**C**), 17.35 (**CH$_3$**-C10), -4.55 (**CH$_3$**-Si), -4.61 (**CH$_3$**-Si).

LRMS (*m/z*): 478 (M^+, 2%), 421 (25), 403 (77), 359 (84), 343 (20), 329 (53), 315 (19), 297 (30), 269 (22), 253 (64), 225 (40), 201 (22), 187 (31), 173 (23), 159 (18), 145 (83), 115 (18), 85 (17), 75 (100), 57 (51).

HRMS (EI): Found 478.2015 (M^+), $C_{24}H_{34}O_8Si$ requires 478.2023

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3496 (br), 2997 (w), 2952 (m), 2931 (m), 2857 (w), 2885 (w), 1764 (s), 1608 (w), 1492 (m), 1467 (w), 1433 (w), 1364 (w), 1327 (m), 1260 (m), 1159 (w), 1112 (m), 1085 (m), 1037 (w), 992 (w), 864 (w), 776 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*SR*, 10*SR*, 11*SR*)-9-(*tert.*-butyldimethylsilyloxy)-10,11-[(thioxomethylene)bis(oxy)]-4,4a,9a-tetrahydro-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



219 **220**

1,1-Thiocarbonyldiimidazole (40 mg, 0.225 mmol) was added to the diol **219** (33 mg, 0.069 mmol) in toluene (10 ml) and heated under reflux for 24 hours. The mixture was filtered though a short pad of silica gel and the solvent was removed under reduced pressure. The residue was chromatographed directly on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the thiocarbonate **220** (9 mg, 28%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.23 (1H, d, $J_{8,7}$ = 8.3 Hz, H-8), 6.96 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 6.71 (1H, d, $J_{5,7}$ = 2.4 Hz, H-5), 5.39 (1H, d, $J_{9,9a}$ = 9.0 Hz, H-9), 5.07 (1H, s, H-11), 4.91 (1H, d, $J_{1,9a}$ = 4.5 Hz, H-1), 4.42 (1H, d, $J_{4a,9a}$ = 10.7 Hz, H-4a), 4.05 (3H, s, COO**CH$_3$**), 3.78 (3H, s, **CH$_3$**O-C6), 3.44 (1H, ddd, $J_{9a,4a}$ = 10.7 Hz, $J_{9a,1}$ = 4.5 Hz, $J_{9a,9}$ = 9.0 Hz, H-9a), 1.01 (3H, s, **CH$_3$**-C10), 0.98 (9H, s, **(CH$_3$)$_3$**-C), 0.27 (3H, s, **CH$_3$**-Si), 0.23 (3H, s, **CH$_3$**-Si).

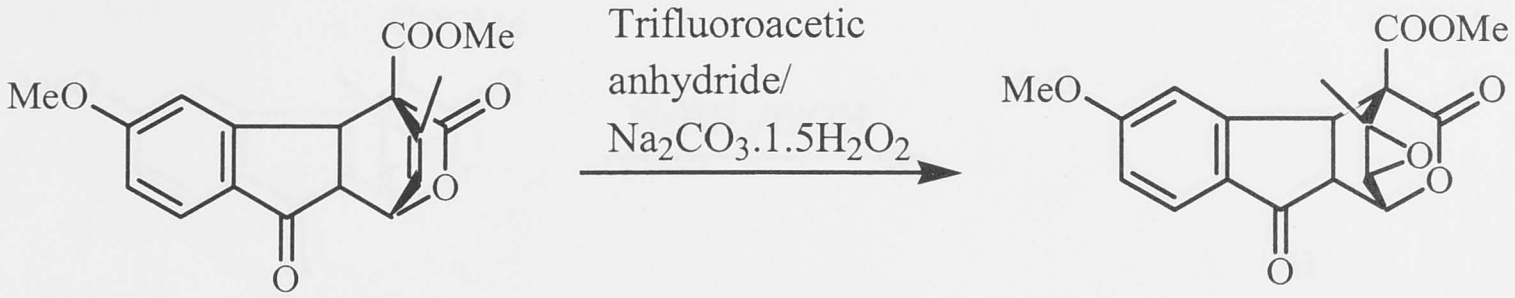
^{13}C-NMR (75MHz, $CDCl_3$): δ 191.82 (**C**=S), 169.47 (C3), 166.50 (C12), 161.00 (C6), 137.54 (C4b), 135.82 (C8a), 126.58 (C8), 116.55 (C5), 110.78 (C7), 88.39 (C11), 82.65 (C10), 73.03 (C9, C1), 61.83 (C4), 55.61 (**CH$_3$**O-C6), 53.72 (COO**CH$_3$**), 43.21 (C9a), 42.50 (C4a), 25.89 (**(CH$_3$)$_3$**-C), 18.09 ((CH$_3$)$_3$-**C**), 14.27 (**CH$_3$**-C10), -4.52 (**CH$_3$**-Si), -4.57 (**CH$_3$**-Si).

LRMS (*m/z*): 520 (M^+, 9%), 459 (2), 388 (2), 343 (5), 313 (3), 267 (6), 219 (4), 178 (7), 157 (33), 149 (54), 133 (31), 105 (34), 91 (100), 93 (27), 72 (27), 57 (66).

HRMS (EI): Found 520.1576 (M^+), $C_{25}H_{32}O_8SiS$ requires 520.1587.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2998 (w), 2950 (w), 2934 (w), 1766 (s), 1607 (w), 1496 (m), 1461 (w), 1434 (w), 1364 (w), 1320 (m), 1264 (m), 1201 (m), 1158 (w), 1112 (m), 1089 (m), 1032 (w), 986 (w), 853 (w), 777 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*SR*, 11*SR*)-10,11-epoxy-1,4,4a,9a-tetrahydro-6-methoxy-3,9-dioxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



137 **225**

Trifluoroacetic anhydride (2.91 ml, 17.3 mmol) was added over 1 hour to the alkene **137** (380 mg, 1.16 mmol) and sodium percarbonate (3.64 g, 23.2 mmol) in dichloromethane (50 ml). Stirring was continued for 12 hours. The mixture was diluted with dichloromethane (100 ml) and washed with 2M HCl (50 ml), water (50 ml), brine (25 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to afford the epoxide **225** (208 mg, 52%) as a colourless oil and starting material (56 mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.75 (1H, d, $J_{8,7}$ = 8.7 Hz, H-8), 7.23 (1H, d, $J_{5,7}$ = 2.1 Hz, H-5), 7.04 (1H, dd, $J_{7,8}$ = 8.7 Hz, $J_{7,5}$ = 2.2 Hz, H-7), 5.26 (1H, dd, $J_{1,9a}$ = 4.9 Hz, $J_{1,11}$ = 3.0 Hz, H-1), 4.39 (1H, d, $J_{4a,9a}$ = 7.7 Hz, H-4a), 4.02 (3H, s, COO**CH_3**), 3.90 (3H, s, **CH_3**O-C6), 3.58 (1H, dd, $J_{9a,4a}$ = 7.7 Hz, $J_{9a,1}$ = 4.8 Hz, H-9a), 3.29 (1H, d, $J_{11,1}$ = 3.0 Hz, H-11), 0.75 (3H, s, **CH_3**-C10).

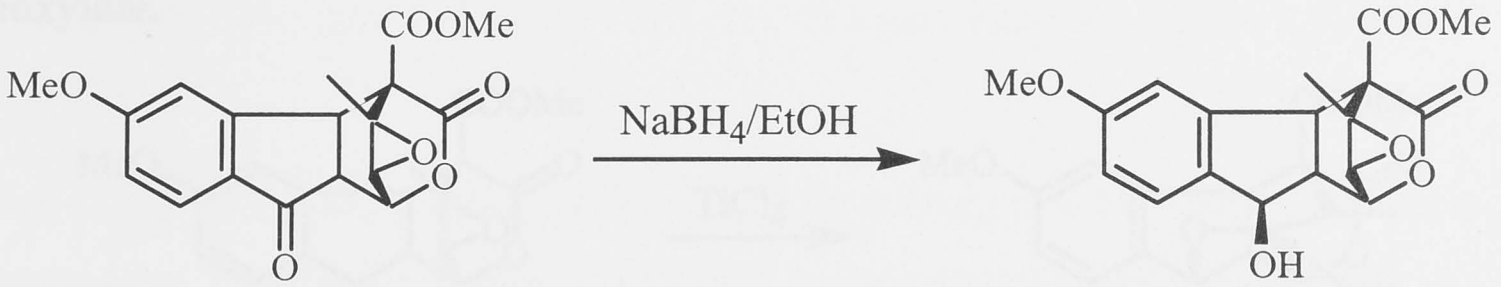
^{13}C-NMR (75MHz, $CDCl_3$): δ 198.90 (C9), 167.34 (C3), 166.92 (C12), 166.33 (C6), 154.55 (C4b), 131.10 (C8a), 126.46 (C8), 117.47 (C5), 111.56 (C7), 70.83 (C1), 62.73 (C4), 56.03 (**CH_3**O-C6), 53.71 (C11), 53.33 (C10), 52.49 (COO**CH_3**), 51.05 (C9a), 40.28 (C4a), 17.77 (**CH_3**-C10).

LRMS (*m/z*): 344 (M^+, 100%), 284 (43), 257 (20), 241 (49), 225 (32), 213 (17), 198 (35), 160 (48), 115 (15), 102 (12), 84 (89), 67 (15).

HRMS (EI): Found 344.0893 (M^+), $C_{11}H_{16}O_7$ requires 344.0896.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2953 (w), 2846 (w), 1770 (s), 1743 (s), 1703 (s), 1596 (s), 1489 (w), 1439 (w), 1382 (w), 1358 (w), 1340 (w), 1305 (w), 1295 (s), 1211 (w), 1170 (w), 1149 (w), 1085 (m), 1055 (w), 1021 (w), 878 (w), 735 (w), 532 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*SR*)-10,11-epoxy-1,4,4a,9a-tetrahydro-9-hydroxy-6-methoxy-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



225 **256**

Sodium borohydride (3 mg, 0.081 mmol) was added to the ketone **225** (28 mg, 0.081 mmol) was dissolved in a 4:1 solution of tetrahydrofuran/ethanol (3 ml) and stirred at room temperature for 3 hours. The mixture was diluted with ethyl acetate (40 ml) and acidified with 2M HCl (5 ml). The organic phase was washed with brine (5 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the alcohol **256** (23 mg, 82%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.29 (1H, d, $J_{8,7}$ = 8.2 Hz, H-8), 6.93 (1H, dd, $J_{7,8}$ = 8.2 Hz, $J_{7,5}$ = 2.3 Hz, H-7), 6.90 (1H, d, $J_{5,7}$ = 2.3 Hz, H-5), 5.47 (1H, d, $J_{9,9a}$ = 9.2 Hz, H-9), 5.11 (1H, dd, $J_{1,9a}$ = 4.0 Hz, $J_{1,11}$ = 3.0 Hz, H-1), 4.15 (1H, d, $J_{4a,9a}$ = 9.3 Hz, H-4a), 4.01 (3H, s, COO**CH$_3$**), 3.78 (3H, s, **CH$_3$**O-C6), 3.68 (1H, d, $J_{11,1}$ = 3.0 Hz, H-11), 3.56 (1H, ddd, $J_{9a,4a}$ = 9.3 Hz, $J_{9a,9}$ = 9.2 Hz, $J_{9a,1}$ = 4.0 Hz, H-9a), 0.89 (3H, s, **CH$_3$**-C10).

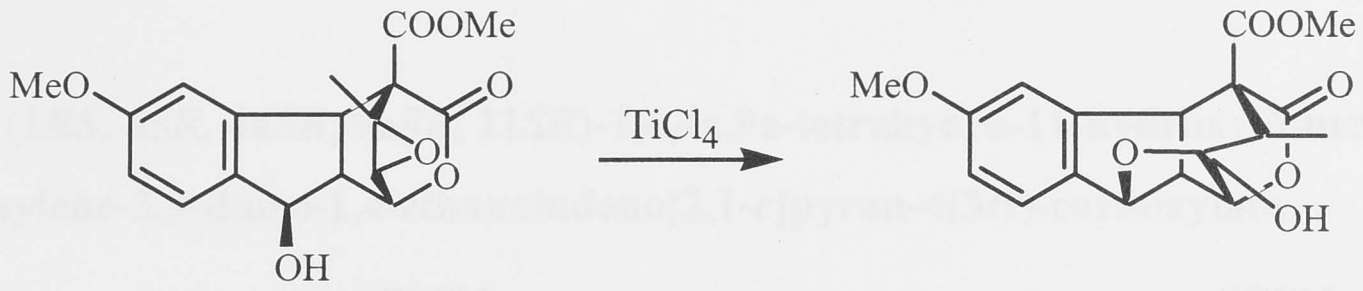
^{13}C-NMR (75MHz, $CDCl_3$): δ 168.10 (C3), 167.89 (C12), 160.76 (C6), 139.82 (C4b), 136.97 (C8a), 126.17 (C8), 115.93 (C5), 110.71 (C7), 72.94 (C1), 72.21 (C9), 62.81 (C4), 55.56 (**CH$_3$**O-C6), 54.70 (C11), 53.21 (C10), 53.10 (COO**CH$_3$**), 45.97 (C9a), 44.46 (C4a), 18.15 (**CH$_3$**-C10).

LRMS (*m/z*): 346 (M^+, 22%), 328 (29), 271 (11), 243 (16), 225 (26), 197 (17), 186 (43), 173 (100), 145 (51), 139 (15), 115 (33), 102 (17), 91 (19), 83 (43), 67 (19).

HRMS (EI): Found 346.1047 (M^+), $C_{18}H_{18}O_7$ requires 346.1053.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3521 (br), 2954 (w), 1755 (s), 1607 (w), 1496 (w), 1436 (w), 1364 (w), 1302 (w), 1275 (m), 1259 (m), 1178 (w), 1150 (w), 1109 (w), 1084 (m), 1049 (w), 1032 (w), 911 (w), 873 (w), 731 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9*RS*, 9a*RS*, 10*SR*, 11*RS*)-9,11-epoxy-1,4,4a,9a-tetrahydro-11-hydroxy-6-methoxy-10-methyl-3-oxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



256 **226**

Titanium tetrachloride (274 mg, 1.44 mmol) was added dropwise over 10 minutes to the epoxide **256** (50 mg, 0.144 mmol) in dichloromethane (5 ml) at 0°C. The mixture was stirred for 30 minutes and then diluted with dichloromethane (50 ml). The organic phase was washed with water (2x10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed to afford a complex mixture. Chromatography on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) yielded the hemi-acetal **226** (1 mg, 4%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.33 (1H, d, $J_{8,7}$ = 8.4 Hz, H-8), 6.87 (1H, dd, $J_{7,8}$ = 8.4 Hz, $J_{7,5}$ = 2.5 Hz, H-7), 6.47 (1H, d, $J_{5,7}$ = 2.2 Hz, H-5), 5.26 (1H, d, $J_{9,9a}$ = 5.3 Hz, H-9), 4.72 (1H, d, $J_{1,9a}$ = 6.2 Hz, H-1), 4.07 (1H, d, $J_{4a,9a}$ = 8.7 Hz, H-4a), 3.93 (3H, s, COO**CH$_3$**), 3.78 (3H, s, **CH$_3$**O-C6), 3.55 (1H, ddd, $J_{9a,4a}$ = 8.8 Hz, $J_{9a,1}$ = 6.0 Hz, $J_{9a,9}$ = 5.4 Hz, H-9a), 2.32 (1H, q, $J_{10,Me}$ = 7.3 Hz, H-10), 1.16 (3H, d, $J_{Me,10}$ = 7.3 Hz, **CH$_3$**-C10).

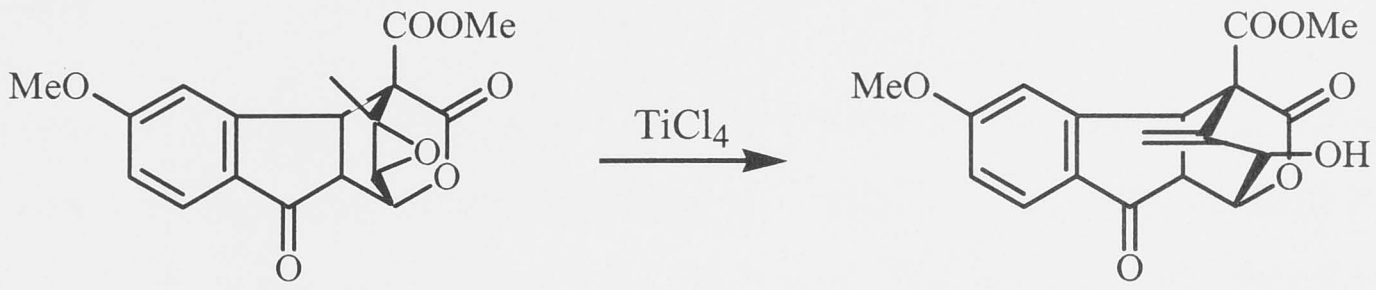
^{13}C-NMR (75MHz, $CDCl_3$): δ 167.94 (C3), 167.67 (C12), 161.19 (C6), 141.65 (C4b), 135.20 (C8a), 126.33 (C8), 115.26 (C5), 110.03 (C7), 102.25 (C11), 84.05 (C1), 78.93 (C9), 57.36 (C4), 55.41 (**CH$_3$**O-C6), 52.49 (COO**CH$_3$**), 49.04 (C9a), 45.46 (C4a), 41.90 (C10), 23.42 (**CH$_3$**-C10).

LRMS (*m/z*): 346 (M^+, 97%), 328 (9), 315 (10), 287 (10), 270 (17), 256 (10), 241 (28), 229 (11), 213 (21), 202 (100), 185 (23), 174 (36), 158 (18), 146 (79), 127 (39), 115 (26), 102 (17), 91 (8).

HRMS (EI): Found 346.1051 (M^+), $C_{18}H_{18}O_7$ requires 346.1053.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3400 (br), 2924 (w), 2850 (w), 2838 (w), 1765 (s), 1740 (s), 1607 (w), 1496 (w), 1436 (w), 1365 (w), 1310 (w), 1257 (s), 1184 (w), 1148 (w), 1112 (w), 1091 (m), 1066 (m), 1053 (m), 1028 (m), 984 (m), 913 (w), 824 (w), 797 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 11*SR*)-1,4,4a,9a-tetrahydro-11-hydroxy-6-methoxy-10-methylene-3,9-dioxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



225 **229**

Titanium tetrachloride (85 mg, 0.448 mmol) was added dropwise to the epoxide **225** (70 mg, 0.203 mmol) in dichloromethane (5 ml) at 0°C and stirred for 1 hour. The mixture was diluted with dichloromethane (50 ml), washed with water (2x10 ml) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the allylic alcohol **229** (53 mg, 76%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.69 (1H, d, $J_{8,7}$ = 8.5 Hz, H-8), 6.99 – 6.95 (2H, m, H-7, H-5), 5.39 (1H, s, **CH_2**=C10), 5.35 (1H, s, **CH_2**=C10), 5.11 (1H, dd, $J_{1,9a}$ = 5.4 Hz, $J_{1,11}$ = 1.4 Hz, H-1), 4.44 (1H, d, $J_{4a,9a}$ = 8.4 Hz, H-4a), 4.01 (3H, s, COO**CH_3**), 3.89 (1H, s, $J_{11,1}$ = 1.4 Hz, H-11), 3.87 (3H, s, **CH_3**O-C6), 3.52 (1H, dd, $J_{9a,4a}$ = 8.5 Hz, $J_{9a,1}$ = 5.4 Hz, H-9a).

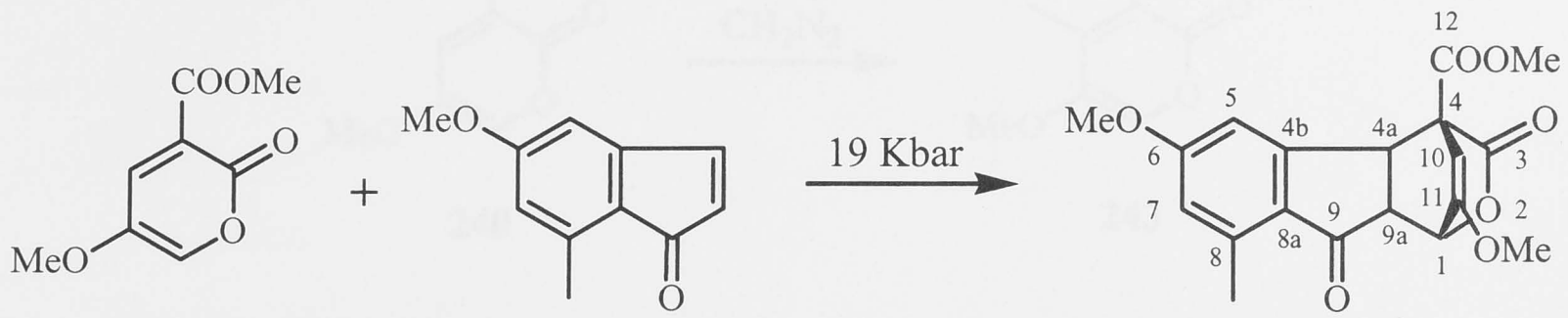
^{13}C-NMR (75MHz, $CDCl_3$): δ 199.04 (C9), 169.03 (C3), 167.89 (C12), 166.51 (C6), 155.00 (C4b), 137.74 (C10), 130.98 (C8a), 126.51 (C8), 121.78 (**CH_2**=C10), 116.95 (C5), 111.27 (C7), 79.72 (C11), 66.71 (C1), 61.75 (C4), 56.07 (**CH_3**O-C6), 53.41 (COO**CH_3**), 49.20 (C9a), 42.46 (C4a).

LRMS (*m/z*): 344 (M^+, 35%), 300 (11), 282 (45), 250 (17), 241 (100), 223 (59), 211 (39), 195 (15), 181 (14), 161 (62), 152 (21), 128 (15), 115 (27), 102 (17), 89 (15), 77 (23), 63 (24).

HRMS (EI): Found 344.0898 (M^+), $C_{18}H_{16}O_7$ requires 344.0896.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3445 (br), 2952 (w), 1762 (s), 1702 (s), 1595 (s), 1488 (w), 1439 (w), 1361 (w), 1340 (w), 1306 (m), 1261 (s), 1161 (w), 1092 (m), 1047 (m), 973 (w), 880 (w), 732 (w).

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*)-1,4,4a,9a-tetrahydro-6,11-dimethoxy-8-methyl-3,9-dioxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



240 **83** **242**

The indenone **83** (15 mg, 0.086 mmol) and the pyrone **240** (4 mg, 0.022 mmol) were dissolved in a minimum of dichloromethane (0.1 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the cycloadduct **242** (5 mg, 64%, based on pyrone) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.68 (1H, s, H-7), 6.63 (1H, s, H-5), 5.26 (1H, dd, $J_{1,9a}$ = 5.1 Hz, $J_{1,10}$ = 2.8 Hz, H-1), 4.95 (1H, d, $J_{10,1}$ = 2.8 Hz, H-10), 4.26 (1H, d, $J_{4a,9a}$ = 7.0 Hz, H-4a), 4.03 (3H, s, COO**CH$_3$**), 3.83 (3H, s, **CH$_3$**O-C6), 3.56 (1H, dd, $J_{9a,4a}$ = 7.0 Hz, $J_{9a,1}$ = 4.9 Hz, H-9a), 3.39 (3H, s, **CH$_3$**O-C11), 2.55 (3H, s, **CH$_3$**-C8).

^{13}C-NMR (75MHz, $CDCl_3$): δ 198.98 (C9), 170.07 (C3), 168.25 (C12), 165.04 (C6), 157.97 (C11), 154.74 (C4b), 141.61 (C8), 129.68 (C8a), 117.78 (C5), 107.30 (C7), 90.89 (C10), 76.74 (C1), 58.03 (C4), 56.22 (**CH$_3$**O-C11), 55.54 (**CH$_3$**O-C6), 53.26 (COO**CH$_3$**), 52.15 (C9a), 40.36 (C4a), 18.56 (**CH$_3$**-C8).

LRMS (*m/z*): 358 (M^+, 20%), 314 (21), 286 (44), 255 (91), 240 (5), 212 (6), 184 (7), 174 (100), 152 (7), 120 (6), 91 (3), 77 (6), 59 (3).

HRMS (EI): Found 358.1051 (M^+), $C_{19}H_{18}O_7$ requires 358.1052.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3100 (w), 2927 (w), 2850 (w), 1768 (s), 1742 (s), 1698 (s), 1650 (w), 1598 (s), 1454 (w), 1378 (w), 1310 (m), 1260 (m), 1225 (w), 1193 (w), 1149 (s), 1085 (w), 1062 (s), 1039 (w), 1016 (w), 991 (w), 866 (w) 832 (w) 792 (w) 773 (w).

Methyl 5-methoxy-4-methyl-2-oxo-2*H*-pyran-3-carboxylate

240 **243**

The pyrone **240** (300 mg, 1.63 mmol) was dissolved in dichloromethane (10 ml) and cooled to 0°C. Ethereal diazomethane was added in portions over 1 hour until all the starting material had been consumed. Stirring at room temperature was continued for a further 16 hours. The solvent was removed under reduced pressure and the residue was chromatographed directly on silica gel (petroleum ether : ethyl acetate = 1:1) to yield the pyrone **243** (244 mg, 75%). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p.: 123-125°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.07 (1H, s, H-6), 3.91 (3H, s, COO**CH_3**), 3.70 (3H, s, **CH_3**O-C5), 2.17 (3H, s, **CH_3**-C4).

^{13}C-NMR (75MHz, $CDCl_3$): δ 164.78 (**C**OOCH_3), 158.05 (C2), 151.17 (C4), 143.05 (C6), 131.29 (C5), 120.04 (C3), 56.39 (**CH_3**O-C5), 52.85 (COO**CH_3**), 14.42 (**CH_3**-C4).

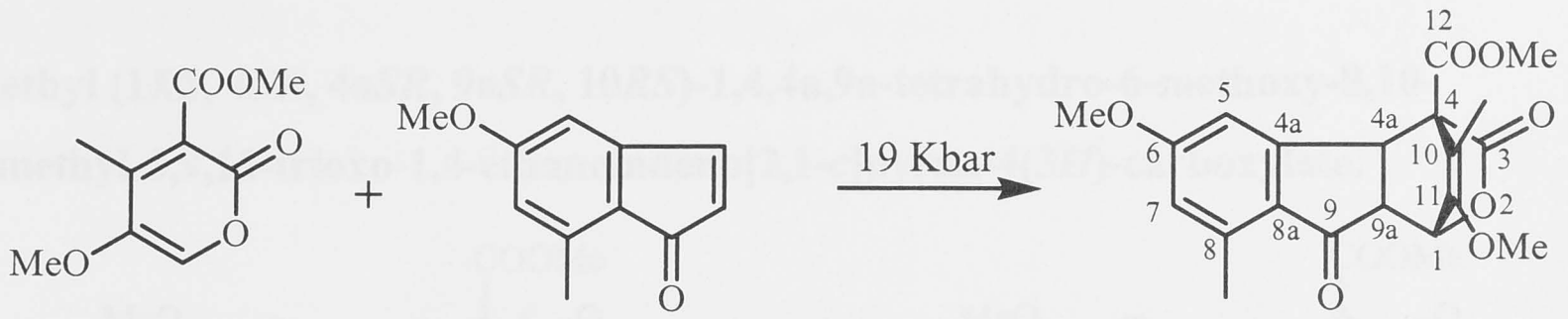
LRMS (*m/z*): 172 (M^+, 72%), 166 (100), 155 (7), 149 (12), 139 (22), 127 (20), 123 (26), 111 (17), 99 (10), 95 (12), 83 (25), 71 (17), 67 (40), 57 (26).

HRMS (EI): Found 198.0530 (M^+), $C_9H_{10}O_5$ requires 198.0528.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3091 (w), 2959 (w), 2852 (w), 1706 (s), 1641 (m), 1546 (m), 1451 (w), 1438 (w), 1416 (w), 1378 (w), 1324 (w), 1301 (m), 1226 (w), 1172 (w), 1116 (w), 1068 (s), 991 (w), 949 (w), 844 (w), 786 (w), 766 (w).

Analysis: Calcd for $C_9H_{10}O_5$: C, 54.55%; H, 5.09%. Found: C, 54.21%; H, 4.84%.

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*)-1,4,4a,9a-tetrahydro-6,11-dimethoxy-8,10-dimethyl-3,9-dioxo-1,4-ethenoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



243 **83** **244**

The indenone **83** (18 mg, 0.010 mmol) and the pyrone **243** (10 mg, 0.05 mmol) were dissolved in a minimum of dichloromethane (0.1 ml). The reaction mixture was then subjected to high pressure (19 Kbar) for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 3:1) to yield the cycloadduct **244** (12 mg, 65%, based on pyrone). Recrystallisation from ethyl acetate afforded colourless crystals.

m.p.: 153-155°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.98 (1H, s, H-7), 6.68 (1H, s, H-5), 5.50 (1H, d, $J_{1,9a}$ = 4.5 Hz, H-1), 4.31 (1H, d, $J_{4a,9a}$ = 6.9 Hz, H-4a), 4.01 (3H, s, COO**CH$_3$**), 3.83 (3H, s, **CH$_3$**O-C6), 3.57 (3H, s, **CH$_3$**O-C11), 3.51 (1H, dd, $J_{9a,4a}$ = 6.9 Hz, $J_{9a,1}$ = 4.7 Hz, H-9a), 2.55 (3H, s, **CH$_3$**-C8), 1.39 (3H, s, **CH$_3$**-C11).

^{13}C-NMR (75MHz, $CDCl_3$): δ 199.53 (C9), 170.29 (C3), 168.21 (C12), 164.89 (C6), 155.28 (C4b), 150.37 (C11), 141.67 (C8), 129.81 (C8a), 117.65 (C5), 112.48 (C10), 108.52 (C7), 73.29 (C1), 61.95 (C4), 57.67 (**CH$_3$**O-C11), 55.62 (**CH$_3$**O-C6), 53.98 (COO**CH$_3$**), 52.82 (C9a), 39.64 (C4a), 18.76 (**CH$_3$**-C8), 12.46 (**CH$_3$**-C10).

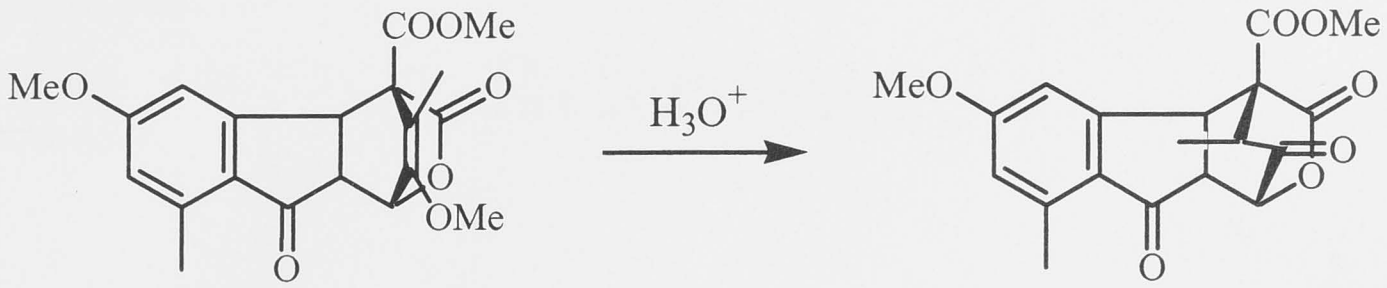
LRMS (*m/z*): 372 (M^+, 10%), 328 (2), 269 (33), 254 (4), 225 (3), 198 (5), 174 (100), 166 (10), 153 (3), 120 (4), 115 (4), 91 (3), 77 (4).

HRMS (EI): Found 372.1210 (M^+), $C_{20}H_{20}O_7$ requires 372.1209.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 3100 (w), 2927 (w), 2850 (w), 1768 (s), 1742 (s), 1698 (s), 1650 (w), 1598 (s), 1454 (w), 1378 (w), 1310 (m), 1325 (m), 1260 (m), 1225 (w), 1193 (w), 1149 (s), 1085 (w), 1062 (s), 1039 (w), 1016 (w), 991 (w), 866 (w) 832 (w) 792 (w) 773 (w).

Analysis: Calcd for $C_{20}H_{20}O_7$: C, 64.51%; H, 5.41%. Found: C, 64.13%; H, 5.52%.

Methyl (1*RS*, 4*SR*, 4a*SR*, 9a*SR*, 10*RS*)-1,4,4a,9a-tetrahydro-6-methoxy-8,10-dimethyl-3,9,11-trioxo-1,4-ethanoindeno[2,1-*c*]pyran-4(3*H*)-carboxylate.



244 **245**

The enol ether **244** (10 mg, 0.027 mmol), trifluoroacetic acid (100 µl) and water (10 µl) in tetrahydrofuran (1 ml) were stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (50 ml), washed with brine (10 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 40-60°C : ethyl acetate = 2:1) to yield the diketone **245** (7 mg, 73%) as a white solid.

m.p.: 228-230°C

^{1}H-NMR (300MHz, $CDCl_3$): δ 6.93 (1H, s, H-7), 6.74 (1H, s, H-5), 5.08 (1H, d, $J_{1,9a}$ = 5.4 Hz, H-1), 4.49 (1H, d, $J_{4a,9a}$ = 8.5 Hz, H-4a), 4.02 (3H, s, COO**CH$_3$**), 3.84 (3H, s, **CH$_3$**O-C6), 3.67 (1H, dd, $J_{9a,4a}$ = 8.6 Hz, $J_{9a,1}$ = 5.4 Hz, H-9a), 3.15 (1H, q, $J_{10,Me}$ = 7.2 Hz, H-10), 2.57 (3H, s, **CH$_3$**-C8), 0.53 (3H, d, $J_{Me,10}$ = 7.2 Hz, **CH$_3$**-C10).

^{13}C-NMR (75MHz, $CDCl_3$): δ 202.90 (C11), 196.63 (C9), 169.75 (C3), 167.69 (C12), 165.52 (C6), 154.88 (C4b), 143.10 (C8), 128.58 (C8a), 118.50 (C5), 109.72 (C7), 81.87 (C1), 59.95 (C4), 56.09 (**CH$_3$**O-C6), 53.83 (COO**CH$_3$**), 51.58 (C9a), 44.24 (C10), 38.63 (C4a), 19.16 (**CH$_3$**-C8), 12.45 (**CH$_3$**-C10).

LRMS (*m/z*): 358 (M^+, 100%), 326 (8), 300 (8), 282 (11), 271 (35), 254 (39), 243 (13), 226 (12), 214 (16), 204 (20), 189 (9), 175 (29), 141 (9), 127 (63), 115 (21), 83 (14), 59 (10).

HRMS (EI): Found 358.1050 (M^+), $C_{19}H_{18}O_7$ requires 358.1053.

IR: ν_{max} ($CHCl_3$) cm^{-1}: 2953 (w), 2845 (w), 1774 (s), 1744 (s), 1700 (s), 1598 (s), 1455 (w), 1437 (s), 1379 (w), 1345 (m), 1312 (m), 1250 (m), 1230 (w), 1192 (w), 1170 (w), 1149 (s), 1101 (w), 1065 (m), 1034 (w), 946 (w), 856 (w), 823 (w), 710 (w).

Analysis: Calcd for $C_{19}H_{18}O_7$: C, 63.68%; H, 5.06%. Found: C, 63.50%; H, 5.33%.

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